08-1136

Industria y Comercio
SUPERINTENDENCIA PROPIEDAD INDUSTRIAL
República de Colombia
Ministerio de Comercio, Industria y Turismo

CSA229923

INVENTARIO

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD DE PCT

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No. 08-1136

54. TITULO: COMPUESTO HETEROCICLICO (Nuevo Título f. 721)
CICLOPROPIL PIRROLIDINAS PARA EL TRATAMIENTO DE ENFERM DE TIPO GLUCOCORTICOIDE

52. CLASIFICACION INTERNACIONAL: C07D 401/14 // A61K31/45 A61K31/4545 // A61K45/00 // A61P3/04 // A61P3/06 // A61K3 A61P3/10 // A61P9/12.

71. SOLICITANTE: JAPAN TOBACCO INC.

DOMICILIO: 2-1, Toranomon 2-chome, Minato-ku, Tokyo 105-8422, JAPON

74. APODERADO: Dra. MARGARITA CASTELLANOS A.

22. BOGOTA, D.C., 18 ENE. 2008
20070108

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-001136- -00000-0000
Fecha: 2008-01-08 16:23:50 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 718

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

SOLICITUD DE:PATENTE EN COLOMBIA

1)

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I [ ] Capítulo II

2) SOLICITANTE (71)

Nombre: **JAPAN TOBACCO INC**

Dirección: **2-1, Toranomon 2-chome**
Minato-ku
Tokyo 105-8422
Japón

Domicilio: **Tokyo 105-8422**
Japón

Lugar de Constitución: **Japón**

Teléfono: Fax:
E-mail:

IDENTIFICACIÓN
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número

3) REPRESENTANTE O APODERADO (74)

Nombre: **MARGARITA CASTELLANOS A.**

Dirección: **CALLE 94A No. 7A-09**

Teléfono: **610 7420** Fax: **610 0706**

E-mail: info@castellanosyco.com

IDENTIFICACIÓN
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número **39'779.654** TPA **70.819**

4) INVENTOR (ES) (72)

VER ANEXO # 1

5) PCT (86)

Solicitud Internacional No. **PCT/JP2006/311975** Fecha **08/06/2006**

Publicación Internacional No. **WO2006/132436 A1** Fecha **14/12/2006**

6) Título (54)

COMPUESTO HETEROCICLICO

7) Clasificación Internacional (51) A61K31/454 // 31/454 C07D 401/14 // A61K45/00 // A61P3/04 A61K31/506 // A61P3/06 // A61P3/10 // A61P9/12

8) Prioridad

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
JP	08/06/2005	2005-168901
US	17/06/2005	60/692,039
JP	03/02/2006	2006-027097
US	13/02/2006	60/772,734
JP	17/05/2006	2006-138252

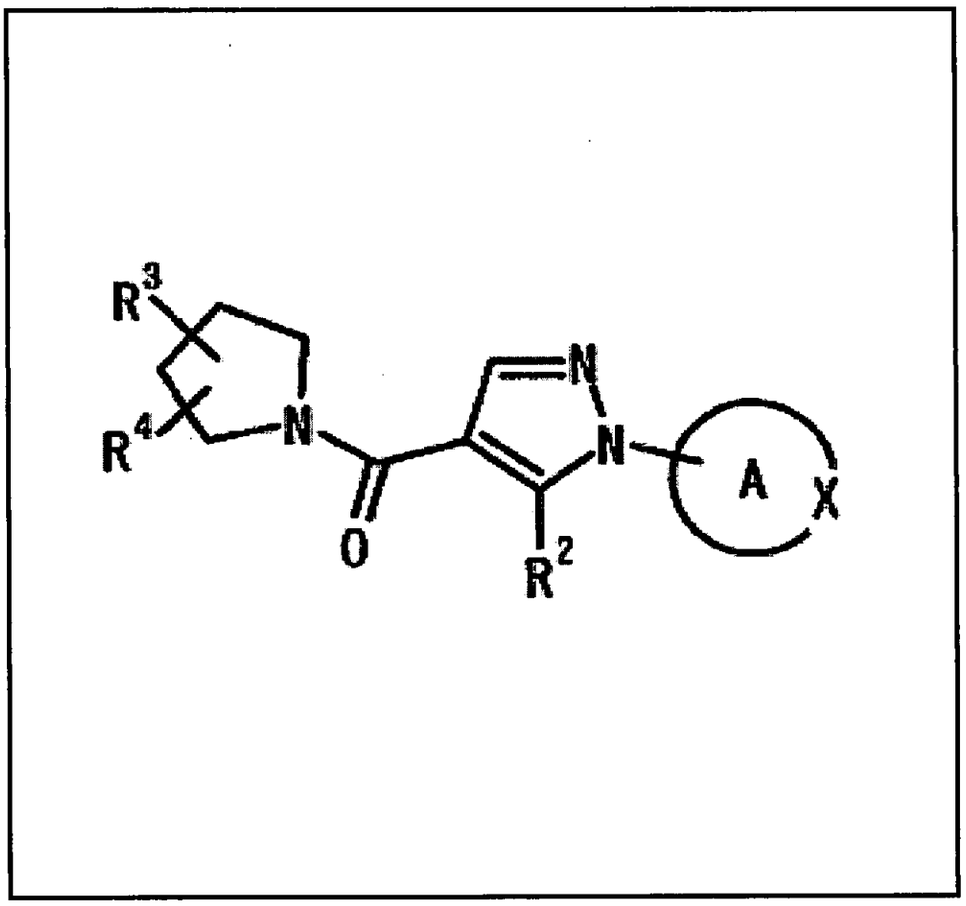
9) Comprobante de pago No. **08-632** **Fecha** **3 de enero de 2008**

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

Anexos

- [ ] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso, junto con la sustitución del mismo a mi favor
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [ ] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional 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 indigenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [ ] Otros **Tarjeta Propietario y Extracto para la Publicación**

FIGURA CARACTERISTICA:



Solicito la concesión de la patente,

NOMBRE: **MARGARITA CASTELLANOS ABONDANO**

FIRMA:

C.C. No. 39.779.654 Usaquén - TPA 70.819 C.S.J.

18 ENE 2008

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página. - MCA/jdf/P1556

ANEXO # 1
INVENTORES

Hiroshi YAMAMOTO
c/o Central Pharmaceutical Research
Institute of Japan Tobacco Inc., 1-1,
Murasaki-cho, Takatsuki-shi
Osaka
Japón

Yasuhiro OHE
c/o Central Pharmaceutical Research
Institute of Japan Tobacco Inc., 1-1,
Murasaki-cho, Takatsuki-shi
Osaka
Japón

Hiroyuki GOTO
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Institute of Japan Tobacco Inc., 1-1,
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c/o Central Pharmaceutical Research
Institute of Japan Tobacco Inc., 1-1,
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Osaka
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Murasaki-cho, Takatsuki-shi
Osaka
Japón

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Murasaki-cho, Takatsuki-shi
Osaka
Japón

Shunsuke FUJII
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Institute of Japan Tobacco Inc., 1-1,
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Kota ASAHINA
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Murasaki-cho, Takatsuki-shi
Osaka
Japón

Takashi ITO
c/o Central Pharmaceutical Research
Institute of Japan Tobacco Inc., 1-1,
Murasaki-cho, Takatsuki-shi
Osaka
Japón

5

'ERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-001136- -00000-0000
Fecha: 2008-01-08 16:23:50 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 718

NIT : 800176089-2

)FICIAL DE CAJA : 08 - 632
: ENERO 3 DE 2008

***** C O N S I G N A C I O N *****

)NTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
:ASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2540893	03/01/2008	3,102,000.00

***** C O N C E P T O *****

(ENTISTICO	CONCEPTO		TOTAL CONCEPTO
30005-01-01 SOLICITUDES	1	TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
		TOTAL : $	501,000.00

)UINIENTOS UN MIL PESOS

)BLE : _____

)E CAJA APLICADO AL EXPEDIENTE No._____

CASTELLANOS & CO.
ABOGADOS
Calle 94 A No. 7 A-09
Apartado 6349
Bogotá, D.C. – COLOMBIA

Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Ref.: **PODER** conferido por la sociedad **JAPAN TOBACCO INC.**

Yo, **XIMENA CASTELLANOS ABONDANO,** mayor de edad, identificada y domiciliada como aparece al pié de mi firma, atentamente manifiesto a Uds. que sustituyo en la Dra. **MARGARITA CASTELLANOS ABONDANO,** el poder que me confirió la sociedad **JAPAN TOBACCO INC.,** con domicilio en **2-1, Toranomon 2-chome, Minato-ku, Tokyo 105-8422, JAPÓN** debidamente legalizado por Apostilla, bajo los Nos. **02041 y 02042** el día **14 de Junio de 2004**, con las mismas facultades que me fueron conferidas, para tramitar la solicitud de Patente PCT Entrada en Fase Nacional en Colombia, para: **"COMPUESTO HETEROCICLICO".-**

Del Señor Jefe,

Ximena Castellanos Abondano
C.C. No. **39.773.330** de Usaquén
T.P.A. No. **58.236** del C.S.J.
Calle 94A No. 7A-09 – Bogotá, D.C.
Teléfonos: 6107420 – 6107480

Acepto

Margarita Castellanos Abondano
C.C. No. **39.779.654** de Usaquén
T.P.A. No. **70.819** del C.S.J.
Calle 94A No. 7A-09 – Bogotá, D.C.
Teléfonos: 6107420 – 6107480

Bogotá, D.C.
XCA/MCA/P1556

G:\USER\DEPARTAMENTO DE PATENTES\PATENTES\15\P1556\MEMORIAL SUSTITUCION PODER.doc

AUTENTICACION DE FIRMA
MEDIANTE COMPARECENCIA PERSONAL
(Art. 84 C.P.C. mod. Decr. 2282 de 1989, art. 1 mod. 36)
Ante mi Notario Cuarenta y Uno (41) del círculo de esta ciudad compareció personalmente:
Ximena Castellanos.
identificado con C.C. 39773339
expedida en: Usaquén y tarjeta profesional de abogado(a) No. 58236 del Consejo Superior de la Judicatura, con documento dirigido a SIC
y declaró que la firma puesta en este escrito es suya.

Firma del declarante

En Bogotá D.C. a 28 DIC. 2007
AUTORIZÓ ESTA DILIGENCIA EL SUSCRITO NOTARIO

REPUBLICA DE COLOMBIA
Círculo de Santafé de Bogotá, D.C.
NOTARIA 41
Carrera 12 No 93-26
AGUSTIN MORALES RIVEIRA

AUTENTICACION DE FIRMA
MEDIANTE COMPARECENCIA PERSONAL
(Art. 84 C.P.C. mod. Decr. 2282 de 1989, art. 1 mod. 36)
Ante mi Notario Cuarenta y Uno (41) del círculo de esta ciudad compareció personalmente:
Margarita Castellanos.
identificado con C.C. 39779054
expedida en: Usaquén y tarjeta profesional de abogado(a) No. 97081 del Consejo Superior de la Judicatura, con documento dirigido a SIC
y declaró que la firma puesta en este escrito es suya.

Firma del declarante

En Bogotá D.C. a 28 DIC. 2007
AUTORIZÓ ESTA DILIGENCIA EL SUSCRITO NOTARIO

REPUBLICA DE COLOMBIA
Círculo de Santafé de Bogotá, D.C.
NOTARIA 41
Carrera 12 No 93-26
AGUSTIN MORALES RIVEIRA

4926-FNPCT, 4929-FNPCT 7

PODER

l (los) suscrito (s) JAPAN TOBACCO INC.

omiciliado (s) en 2-1, Toranomon 2-chome, Minato-ku, Tokyo 105-8422 - JAPON

ombra(n) por el presente a **XIMENA CASTELLANOS A.** y/o **ARGARITA CASTELLANOS A.** abogadas con oficinas en la Carrera 9 No. 93-, Bogotá - Colombia para

ara obtener la protección de mi (nuestra) propiedad industrial y con este autorizamos a dichos apoderados para que nos representen ante alesquiera autoridades o personas de los órdenes administrativo, ntencioso-administrativo y judicial en todo lo relacionado con los siguientes os y gestiones:

Obtención de patentes de invención , modelos y dibujos industriales; istro de marcas de fábrica, de servicio, colectivas o defensivas y de ominaciones de origen; depósito de nombres y enseñas comerciales; su ovación prórroga, inscripción de traspaso y cambio de nombre o domicilio, celación voluntaria y el registro de licencias de uso de esos derechos; ara la obtención de Registros Sanitarios; c) Acciones de oposición, ervación, cancelación, nulidad, medidas cautelares y en general los juicios es, penales, administrativos o contencioso-administrativos que novamos o se nos promuevan, pudiendo en todos los actos y gestiones a determinados sustituir éste mandato, transigir, desistir, recibir, cancelar, nciar, aceptar notificaciones y nombrar apoderados judiciales y judiciales.

y firmado hoy 7 de Junio de 2004

Tokyo, JAPON

Teruo DAITO

ry should execute on other side)
ular legalization necessary)

POWER OF ATTORNEY

I (we) the undersigned Japan Tobacco Inc.

of 2-1, Toranomon 2-chome, Minato-ku, Tokyo 105-8422 Japan

hereby grant(s) Power of Attorney to **XIMENA CASTELLANOS A.** and/or **MARGARITA CASTELLANOS A.** attorneys residing at Carrera 9 No. 93-09 Bogotá - COLOMBIA to

and to obtain the protection of my (our) industrial property, for which purpose we authorize the said attorneys to represent us before any authorities or persons , specially those, administrative contentious and judicial, in all matters concerning the following :

a) Obtention of patents, models and designs; registration of trademarks, service, collective and defensive marks, and of designations of origin; the deposit of commercial names and ensigns; its renewal , extension, recordal of assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rigths; b) For de obtention of Sanitary Registrations; c) Actions of opposition, cancellation, nullity, infringement, granting of licenses; and in general the civil, criminal and administrative suits related to those rigths; actions and suits instituted by us or against us; and that in all the above matters they may substitute this Power of Attorney, compromise, desist, cancel, receive, renounce, accept notifications and appoint attorneys in fact, in or out of Court .

Given and signed this June 7, 2004

in Tokyo - JAPAN

By Japan Tobacco Inc.

Teruo DAITO, Patent Attorney
General Manager,
Patent Information Dept.

(Notary should execute on other side)
(Consular legalization necessary)

ALVARO CASTELLANOS M.&CIA.
ABOGADOS COLOMBIA
Carrera 9 No. 93-09 - P.O. Box 6349 - Bogotá, Colombia.
Tels.: (571) 610 7420 /60 / 80 - Fax. (571) 610 0706 - e-mail acastell@impsat.net.co

Esta copia coincide con el original que tuve a la vista.
Bogotá, D.C.
28 DIC 2007
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

8

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: **JAPAN**

   This public document

2. has been signed by — Katsuyuki YAMAGUCHI
3. acting in the capacity of — Notary Public of the Osaka Legal Affairs Bureau
4. bears the seal/stamp of — Katsuyuki YAMAGUCHI, Notary Public

Certified

5. at **Osaka**
6. JUN. 14. 2004
7. by **the Ministry of Foreign Affairs**
8. No. 02041
9. Seal/stamp:
10. Signature:

Tsutomu HIGUCHI
For the Minister for Foreign Affairs

Esta copia coincide con el original que tuve a la vista.
Bogotá, D.C.
28 DIC 2007
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

認証登簿平成１６年第100号

嘱託人大東輝雄は、本公証人の面前で、別紙編綴の書面に署名した。

よって、これを認証する。

平成１６年３月３１日、本職の役場において。

大阪府高槻市芥川町１丁目１５番１８号(ミドリ芥川ビル内)

大阪法務局所属

公証人　山口勝之

Registerd No100(2004)

NOTARIAL CERTIFICATE

This is to certify that Teruo DAITO signed the attached document in my very presence on this 31st day of March 2004.

Katsuyuki Yamaguchi

Katsuyuki Yamaguchi
Notary, attached to
Osaka Legal affairs Bureau
15-18,1-chome,Akutagawa-cho,
Takatsuki-shi,Osaka,Japan.

OSAKA LEGAL AFFAIRS BUREAU
NOTARY
15-18,(Midori Akutagawa Bldg.)1-chome
Akutagawa-cho,Takatsuki-shi,Osaka,Japan

大阪法務局所属　公証人役場

Esta copia coincide con el original que tuve a la vista.
Bogotá, D.C.
28 DIC 2007
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

証明書

東京都港区虎ノ門二丁目２番１号を本店所在地とする日本国法人日本たばこ産業株式会社の代表取締役社長である私 本田勝彦 は、該法人を代表して知的財産権に係わる書類を署名作成する権限を有するものであることをここに宣言し、これをもって、２００４年３月３１日当時、該法人の医薬総合研究所特許情報室長職にあった大東輝雄　氏が、代理人に指名され、該法人名義にて外国に提出する特許、実用新案登録の出願等手続に要する願書、委任状、譲渡書、授権書、申請書、請求書、その他を含む関係書類について該法人を代表して署名、押印、作成する権限を有していたものであることを証明する。

２００４年６月７日

日本たばこ産業株式会社

代表取締役社長　本田　勝彦

Esta copia coincide con el original que tuve a la vista.

28 DIC 2007

AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

CERTIFICATE

I, KATSUHIKO HONDA, President and Chief Executive Officer of JAPAN TOBACCO INC., a Japanese corporation located at 2-1, TORANOMON 2-CHOME, MINATO-KU, TOKYO 105-8422, JAPAN, hereby declare that I am authorized to sign and execute documents relating to intellectual property rights on behalf of the said corporation, and hereby certify that, as of March 31, 2004, Mr. TERUO DAITO was Director of Patent Information Dept. of Central Pharmaceutical Research Institute of the said corporation, was my proxy, and was authorized to sign and execute documents relating to intellectual property rights on behalf of the said corporation. Said documents include, but are not limited to, applications, powers of attorney, assignments, authorizations of agents, petitions and the like in connection with patent and utility model filed in foreign countries with the name of the said corporation.

Dated this 7 day of June, 2004,
JAPAN TOBACCO INC.

KATSUHIKO HONDA
President and Chief Executive Officer

Esta copia coincide con el original que tuve a la vista.
Bogotá, D.C.
28 DIC 2007
AGUSTIN MORALES RIVEIRO
NOTARIO CUARENTA Y UNO

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: **JAPAN**

   This public document

2. has been signed by — Katsuyuki YAMAGUCHI
3. acting in the capacity of — Notary Public of the Osaka Legal Affairs Bureau
4. bears the seal/stamp of — Katsuyuki YAMAGUCHI, Notary Public

Certified

5. at **Osaka**
6. JUN. 14. 2004
7. by **the Ministry of Foreign Affairs**
8. No. 02042
9. Seal/stamp:
10. Signature:

Tsutomu HIGUCHI
For the Minister for Foreign Affairs

Esta copia coincide con el original que tuve a la vista.
Bogotá,
28 DIC 2007
ACUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

登簿番号平成１６年第１６８号

日本国法律に従い設立され、日本国東京都港区虎ノ門二丁目２番１号に所在する日本たばこ産業株式会社において、２００４年３月３１日当時、医薬総合研究所特許情報室長職にあった大東輝雄氏が、該法人名義で知的財産関係書類について該法人を代表して署名押印、作成する権限を有していたこと及び同氏が２００４年３月３１日、本職の面前で別紙書類に署名したことを証明する。

よって、ここにこれを認証する。

平成１６年６月８日、本職の役場において。

大阪府高槻市芥川町１丁目１５番１８号（ミドリ芥川ビル）

大阪法務局所属（高槻公証役場）

公証人　山口勝之

Esta copia coincide con el original que tuve a la vista.
Bogotá,
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

大阪法務局所属公証人役場

Registration Book No.168 (2004)

NOTARIAL CERTIFICATE

This is to certify that :

1) Teruo Daito was Director of Patent Information Dept. of Central Pharmaceutical Reseearch Institute of JAPAN TOBACCO INC. ,a Japanese corporation of being legally constituted and in existance in accordance with the laws of Japan ,located at 2-1, Toranomon2-chome, Minato-ku, Tokyo 105-8422 Japan ,as of March 31,2004 and was authorized to sign and execute documents relating to intellectual property rights on behalf of the said corporation.

2) said Teruo Daito signed the attaced document in my presence on 31st day of March,2004.

IN TESTIMONY WHEREOF,I have hereto subscribed my name and affixed my seal of office.

On the 8th day of June,2004
at the Office of Notary Katsuyuki Yamaguchi

Katsuyuki Yamaguchi

Katsuyuki Yamaguchi
Notary,attached to
Osaka Legal affairs Bureau,
15-18,1-chome,Akutagawacho,
Takatsuki-shi, Osaka,Japan.

OSAKA LEGAL AFFAIRS BUREAU
NOTARY
15-18,(Midori Akutagawa Bldg.)1-chome
Akutagawa-cho,Takatsuki-shi,Osaka,Japan

Esta copia coincide con el original que tuve a la vista.
Bogotá, D.C.
28 DIC 2007
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

総第 1558 号

証　　明

大阪法務局所属公証人　山口勝之

平成 16 年 3 月 31 日付

平成 16 年 登簿 第 100 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 6 月 14 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. 6.14

Director of the Osake Legal Affairs Bureau

28 DIC 2007

AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

総第 1559 号

証　　明

大阪法務局所属公証人　山口勝之

平成 16年 6 月 8 日付

平成16年 登簿 第 168 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6月14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. 6.14

Director of the Osake Legal Affairs Bureau

Esta copia coincide con el original que tuve a la vista.
28 DIC 2007

----------TRADUCCION OFICIAL No. 04-0616----------

de un documento escrito en INGLES, el cual para su identificación lleva el sello de la Traductora e Intérprete Oficial, Res. 2755/68 y 01144/97 de Minjusticia, al igual que la presente.----------

(Anexo a un documento de poder otorgado por Japan Tobacco Inc.)

Registro No. 100 (2004)

CERTIFICADO NOTARIAL

La presente es para certificar que Teruo DAITO firmó el documento adjunto en mi propia presencia hoy día 31 de marzo de 2004.

(fdo) ilegible

Katsuyuki Yamaguchi

Notario adjunto a la Oficina de Asuntos Legales de Osaka – 15-18, 1-chome, Akutagawa-cho, Takatsuki-shi, Osaka, Japón

(Sello) Oficina de Asuntos Legales de Osaka

NOTARIO – 15-18 (Midori Akutagawa Bldg) 1-chome

Akutagawa-cho, Takatsuki-shi, Osaka, Japón

APOSTILLA

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

1. País: JAPON

Este documento público

2. ha sido firmado por Katsuyuki YAMAGUCHI
3. actuando en su carácter de Director de la Oficina de Asuntos legales de Osaka



4. lleva el sello de Katsuyuki YAMAGUCHI, Notario Público

Certificado

5. en Osaka 6. el 14 de Junio 2004

7. por el Ministerio de Relaciones Exteriores

8. No. 02041

9. Sello: 10: Firma

(fdo) ilegible

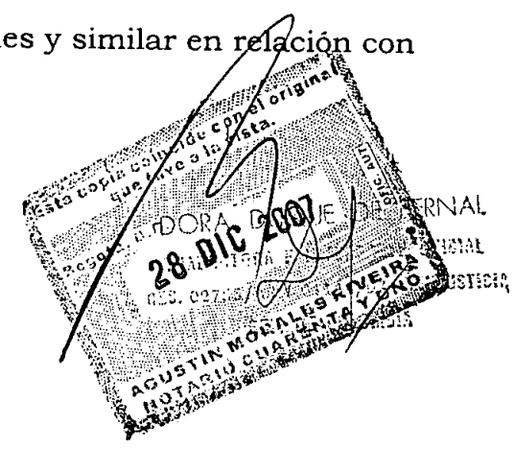
Tsutomu HIGUCHI

Por el Ministro de Relaciones Exteriores.

(Sello del Ministerio de Relaciones Exteriores de Japón)

CERTIFICADO

Yo, KATSUHIKO HONDA, Presidente y Funcionario jefe Ejecutivo de JAPAN TOBACCO INC., una sociedad japonesa situada en 2-1, TORANOMON 2-CHOME, MINATO-KU, TOKYO 105-8422, JAPON, declaro por medio del presente que estoy autorizado para firmar y otorgar documentos relacionados con derechos de propiedad intelectual en nombre de dicha sociedad, y por medio del presente certifico que, a Marzo 31 de 2004, el señor TERUO DAITO era el Director del Departamento de Información de Patentes del Instituto Central de Investigaciones Farmacéuticas de dicha sociedad, era mi apoderado y estaba autorizad para firmar y otorgar documentos relacionados con derechos de propiedad intelectual en nombre de dicha sociedad. Dichos documentos incluyen, pero no se limitan a, solicitudes, poderes, cesiones, autorizaciones de agentes, peticiones y similar en relación con



patentes y modelos de utilidad presentados en países extranjeros con el nombre de dicha sociedad.

Dado hoy día 7 de Junio de 2004

JAPAN TOBACCO INC.

KATSUHIKO HONDA

Presidente y Funcionario Jefe Ejecutivo

Libro de Registro No. 168 (2004)

CERTIFICADO NOTARIAL

La presente es para certificar que:

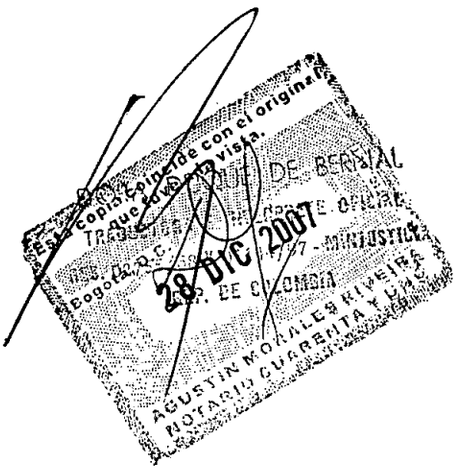
1) Teruo Daito era el Director del departamento de Información de Patentes del Instituto Central de Investigaciones Farmacéuticas de JAPAN TOBACCO INC., una sociedad japonesa que están legalmente constituida y existe de acuerdo con las leyes del Japón, situada en 2-1, Toranomon 2-chome, Minato-ku, Tokio 105-8422 Japón, a Marzo 31 de 2004, y estaba autorizado para firmar y otorgar documentos relacionados con derechos de propiedad intelectual en nombre de dicha sociedad.
2) Dicho Tereuo Daito firmó el documento adjunto en mi propia presencia el día 31 de Marzo de 2004.

EN TESTIMONIO DE LO CUAL, he suscrito aquí mi nombre y he fijado mi sello de oficio.

El día 8 de Junio de 2004

En la Oficina del Notario Katsuyuki Yamaguchi

(fdo) ilegible



Katsuyuki Yamaguchi

Notario adjunto a la Oficina de Asuntos Legales

De Osaka, 15-18, 1-chome, Akutagawacho

Takatsuki-shi; Osaka, Japón

(Sello) Oficina de Asuntos Legales de Osaka

NOTARIO – 15-18 (Midori Akutagawa Bldg) 1-chome

Akutagawa-cho, Takatsuki-shi, Osaka, Japón

CERTIFICADO 1558

La presente es para certificar que la firma que aparece anteriormente ha sido impuesta por Notario, debidamente autorizado y en ejercicio en Osaka, Japón y que el sello oficial que aparece en el mismo es auténtico.

Fecha: 04.6.14

Director de la Oficina de Asuntos Legales de Osaka

CERTIFICADO 1559

La presente es para certificar que la firma que aparece anteriormente ha sido impuesta por Notario, debidamente autorizado y en ejercicio en Osaka, Japón y que el sello oficial que aparece en el mismo es auténtico.

Fecha: 04.6.14

Director de la Oficina de Asuntos Legales de Osaka

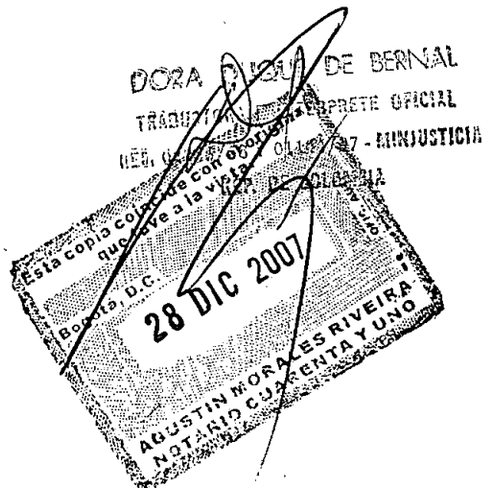
APOSTILLA

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

5. País: JAPON

Este documento público

6. ha sido firmado por Katsuyuki YAMAGUCHI



7. actuando en su carácter de Director de la Oficina de Asuntos legales de Osaka

8. lleva el sello de Katsuyuki YAMAGUCHI, Notario Público

Certificado

5. en Osaka 6. el 14 de Junio 2004

7. por el Ministerio de Relaciones Exteriores

8. No. 02042

9. Sello: 10: Firma

(fdo) ilegible

Tsutomu HIGUCHI

Por el Ministro de Relaciones Exteriores.

(Sello del Ministerio de Relaciones Exteriores de Japón)

Es traducción fiel y completa, a la cual me remito,

Bogotá, Junio 22, 2004.

DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 02755/68 Y 01144/97 - MINJUSTICIA
REP. DE COLOMBIA

Esta copia concuerda con el original que tuve a la vista.
Bogotá, D.C.
28 DIC 2007
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

NO SE ASUME RESPONSABILIDAD

23

2004 JUN

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SANTAFE



EXTERIORES

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CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

RESPONSABILIDAD DEL TEXTO

2004 JUN 24 A 11: 23

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

CESION

El (los) suscrito (s)
HIROSHI YAMAMOTO, YASUHIRO OHE, HIROYUKI GOTO, KAZUHITO HARADA, SHINJI YATA, JUN NISHIU, MAKOTO KAKUTANI, SHUNSUKE FUJII, KOTA ASAHINA, y TAKASHI ITO

en consideración al pago de la suma de (..... US $ 1.oo .....), que he(mos) recibido, por el presente documento cedo (cedemos) a
JAPAN TOBACCO INC.

una compañía constituida de conformidad con las leyes de
JAPON

con oficinas en 2-1, Toranomon 2-chome, Minato-ku, Tokyo 105-8422, JAPON

todos los derechos y títulos sobre la invención nominada

COMPUESTO HETEROCICLICO

EL CESIONARIO firma también el presente y declara que acepta dicha cesión

Dado y firmado hoy 31 de Octubre de 2007

en Osaka, JAPON

ASSIGNMENT

The undersigned

Hiroshi YAMAMOTO, Yasuhiro OHE, Hiroyuki GOTO, Kazuhito HARADA, Shinji YATA, Jun NISHIU, Makoto KAKUTANI, Shunsuke FUJII, Kota ASAHINA and Takashi ITO

in consideration of the sum of (..... US $ 1.oo .....), the receipt of which is hereby acknowledged, by these presents do sell, assign and transfer unto
Japan Tobacco Inc.

a corporation organized under the laws of

Japan

having a place of business at
2-1, Toranomon 2-chome,
Minato-ku, Tokyo 105-8422 Japan
all rights and title to the invention related to

HETEROCYCLIC COMPOUND

THE ASSIGNEE signs these presents and declares that accepts the aforesaid assignment

Given an signed this October 31,2007

in Osaka, JAPON

Inventors

Hiroshi Yamamoto
Hiroshi YAMAMOTO

Yasuhiro Ohe
Yasuhiro OHE

Hiroyuki Goto
Hiroyuki GOTO

Kazuhito Harada
Kazuhito HARADA

Shinji Yata
Shinji YATA

Jun Nishiu
Jun NISHIU

Makoto KAKUTANI

Shunsuke Fujii
Shunsuke FUJII

Kota Asahina
Kota ASAHINA

Takashi Ito
Takashi ITO

Esta copia coincide con el original que tuve a la vista.
Bogotá, D.C.
17 DIC 2007
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

Assignee

Japan Tobacco Inc.

Yoshinori INUBUSHI
Vice President, Intellectual Property

ALVARO CASTELLANOS M. & CIA.
ABOGADOS COLOMBIA

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: **JAPAN**

   This public document

2. has been signed by — Katsuyuki YAMAGUCHI

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

4. bears the seal/stamp of — Katsuyuki YAMAGUCHI, Notary Public

Certified

5. at **Osaka**

6. OCT. 31. 2007

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

8. No. **5089**

9. Seal/stamp:

10. Signature:

Toshihiko TANAKI

For the Minister for Foreign Affairs

Esta copia coincide con el original que tuve a la vista.

Bogotá, D.C.

17 DIC 2007

AGUSTIN MORALES RIVEIRA

NOTARIO CUARENTA Y UNO

認証登簿平成１９年第２８８号

嘱託人犬伏吉則、同山本浩史、同大江泰弘、同後藤浩之、同原田一人、同矢田伸二、同伊東敬史、同西宇淳、同角谷真、同藤井俊介及び同朝比奈幸太は、本公証人の面前で、別紙編綴の書面に署名した。

よって、これを認証する。

平成１９年１０月２４日、本職の役場において。

大阪府高槻市芥川町１丁目１５番１８号(ミドリ芥川ビル内)

大阪法務局所属

公証人　山口勝之

Registerd No.288(2007)

NOTARIAL CERTIFICATE

This is to certify that Yoshinori Inubushi, Hiroshi Yamamoto, Yasuhiro Ohe, Hiroyuki Goto, Kazuhito Harada, Shinji Yata, Takashi Ito, Jun Nishiu, Makoto Kakutani, Shunsuke Fujii and Kota Asahina signed the attached document in my very presence on this 24th day of October, 2007.

Katsuyuki Yamaguchi

OSAKA LEGAL AFFAIRS BUREAU
NOTARY
15-18,(Midori Akutagawa Bldg.)1-chome
Akutagawa-cho,Takatsuki-shi,Osaka,Japan

Katsuyuki Yamaguchi
Notary, attached to
Osaka Legal Affairs Bureau
15-18,1-chome,Akutagawa-cho,
Takatsuki-shi,Osaka,Japan.

大阪法務局所属　公証人役場

Esta copia coincide con el original que tuve a la vista.
Bogotá, D.C.
17 DIC 2007
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

総 第 4131 号

証 明

大阪法務局所属公証人 山口勝之

平成 19年 10月 24日付

平成19年 登簿 第 288 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19年10月31日
平成 年 月 日

大阪法務局長 髙野 伸

CERTIFICATE

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

Date 07.10.31

Director of the Osaka Legal Affairs Bureau

Esta copia coincide con el original que tuvo a la vista.
Bogotá, D.C.
17 DIC 2007
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

----------TRADUCCION OFICIAL No. 07-1207----------

de un documento escrito en INGLES, el cual para su identificación lleva el sello de la Traductora e Intérprete Oficial, Res. 2755/658 y 01144/97 de Minjusticia, al igual que la presente.----------

(Anexos a un documento de cesión otorgado por Hiroshi YAMAMOTO, Yasuhito OHE, Hiroyuki GOTO, Kazuhito HARADA, Shinji YATA, Jun NISHIU, Makoto KAKUTANI, Shunsuke FUJII, Kota ASAHINA, Takashi ITO a favor de Japan Tobacco, Inc.)

CERTIFICADO NOTARIAL

REGISTRO NUMERO 288 (2007)

Por medio del presente certifico que Yoshinori INOBUSHI, **Hiroshi YAMAMOTO, Yasuhiro OHE, Hiroyuki GOTO, Kazuhito HARADA, Shinji YATA, Jun NISHIU, Makoto KAKUTANI, Shunsuke FUJII, y Kota ASAHINA,** firmaron el documento adjunto en mi propia presencia hoy día 24 de Octubre de 2007.

(fdo) Katsuyuki Yamaguchi

Katsuyuki Yamaguchi

Notario adjunto a la

Oficina de Asuntos Legales de Osaka

15-18, 1-chome, Akutagawa-cho,

Takatsuki-shi, Osaka, Japón

(Sello) Oficina de Asuntos Legales de Osaka

NOTARIO - 15-18, 1-chome, Akutagawa-cho, Takatsuki-shi, Osaka, Japón

CERTIFICADO

Esta copia coincide con el original que tuve a la vista.
Bogotá, D.C.
17 DIC 2007
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

Certificamos por la presente que el Certificado Notarial anexo ha sido otorgado por Notario debidamente autorizado y en ejercicio en Osaka, Japón y que el sello oficial que aparece en el mismo es auténtico.

Fecha: 07.10.31

Director de la Oficina de Asuntos Legales de Osaka

APOSTILLA

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

1. País: JAPON

Este documento público

2. ha sido firmado por Katsuyuki YAMAGUCHI

3. actuando en el cargo de Director de la Oficina de Asuntos Legales de Osaka

4. lleva el sello de Katsuyuki YAMAGUCHI, Notario Público

Certificado

5. en Osaka 6. Octubre 31, 2007

7. por el Ministerio de Relaciones Exteriores

8. No. 5089

9. Sello: (del Ministerio de Relaciones Exteriores)

10. Firma: Toshihiko TANAKI

TOSHIHIKO TANAKI

Por el Ministerio de Relaciones Exteriores

ES TRADUCCION FIEL Y COMPLETA, a la cual me remito,

DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 02755/68 Y 01144/97 - MINJUSTICIA
REP. DE COLOMBIA

Esta copia coincide con el original que tuve a la vista.
Bogotá, D.C.
07 DIC 2007
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

(12) 特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
2006 年12 月14 日 (14.12.2006)

PCT

(10) 国際公開番号
WO 2006/132436 A1

(51) 国際特許分類:
C07D 401/14 (2006.01) *A61P 9/12* (2006.01)
A61K 31/454 (2006.01) *A61P 43/00* (2006.01)
A61K 31/4545 (2006.01) *C07D 409/14* (2006.01)
A61K 31/506 (2006.01) *C07D 417/14* (2006.01)
A61K 45/00 (2006.01) *C07C 205/53* (2006.01)
A61P 3/04 (2006.01) *C07D 207/277* (2006.01)
A61P 3/06 (2006.01) *C07D 207/26* (2006.01)
A61P 3/10 (2006.01) *C07D 207/08* (2006.01)

(21) 国際出願番号: PCT/JP2006/311975

(22) 国際出願日: 2006 年6 月8 日 (08.06.2006)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

(30) 優先権データ:
特願2005-168901 2005 年6 月8 日 (08.06.2005) JP
60/692,039 2005 年6 月17 日 (17.06.2005) US
特願2006-027097 2006 年2 月3 日 (03.02.2006) JP
60/772,734 2006 年2 月13 日 (13.02.2006) US
特願2006-138252 2006 年5 月17 日 (17.05.2006) JP

(71) 出願人 (米国を除く全ての指定国について): 日本たばこ産業株式会社 (JAPAN TOBACCO INC.) [JP/JP]; 〒1058422 東京都港区虎ノ門二丁目２番１号 Tokyo (JP).

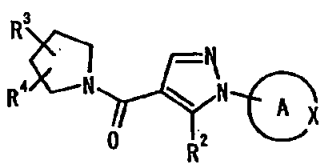
(72) 発明者; および

(75) 発明者/出願人 (米国についてのみ): 山本 浩史 (YAMAMOTO, Hiroshi) [JP/JP]; 〒5691125 大阪府高槻市紫町１番１号 日本たばこ産業株式会社 医薬総合研究所内 Osaka (JP). 大江 泰弘 (OHE, Yasuhiro) [JP/JP]; 〒5691125 大阪府高槻市紫町１番１号 日本たばこ産業株式会社 医薬総合研究所内 Osaka (JP). 後藤 浩之 (GOTO, Hiroyuki) [JP/JP]; 〒5691125 大阪府高槻市紫町１番１号 日本たばこ産業株式会社 医薬総合研究所内 Osaka (JP). 原田 一人 (HARADA, Kazuhito) [JP/JP]; 〒5691125 大阪府高槻市紫町１番１号 日本たばこ産業株式会社 医薬総合研究所内 Osaka (JP). 矢田 伸二 (YATA, Shinji) [JP/JP]; 〒5691125 大阪府高槻市紫町１番１号 日本たばこ産業株式会社 医薬総

[続葉有]

(54) Title: HETEROCYCLIC COMPOUND

(54) 発明の名称: 複素環化合物

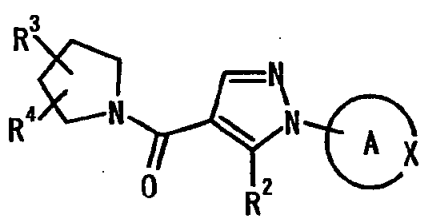


[1']

(57) Abstract: A compound represented by the general formula (1') or a salt thereof; and a therapeutic or prophylactic agent for a glucocorticoid-related condition or an 11 β HSD1 inhibitor comprising the compound of the salt thereof: (1') wherein the ring A, R^2, R^3, R^4 and X are as defined in the description.

(57) 要約:

下記一般式［１’］で表される化合物又はその塩：



[1']

［式中、環Ａ、Ｒ^2、Ｒ^3、Ｒ^{4}及びＸは、明細書中で定義した通りである］、ならびに、当該化合物又はその塩を含有する、グルココルチコイドが関与する病態の治療剤又は予防剤、或いは１１βＨＳＤ１阻害剤を提供する。

WO 2006/132436 A1

合研究所内 Osaka (JP). 西宇 淳 (NISHIU, Jun) [JP/JP]; 〒5691125 大阪府高槻市紫町１番１号 日本たばこ産業株式会社 医薬総合研究所内 Osaka (JP). 角谷 真 (KAKUTANI, Makoto) [JP/JP]; 〒5691125 大阪府高槻市紫町１番１号 日本たばこ産業株式会社 医薬総合研究所内 Osaka (JP). 藤井 俊介 (FUJII, Shunsuke) [JP/JP]; 〒5691125 大阪府高槻市紫町１番１号 日本たばこ産業株式会社 医薬総合研究所内 Osaka (JP). 朝比奈 幸太 (ASAHINA, Kota) [JP/JP]; 〒5691125 大阪府高槻市紫町１番１号 日本たばこ産業株式会社 医薬総合研究所内 Osaka (JP). 伊東 敬史 (ITO, Takashi) [JP/JP]; 〒5691125 大阪府高槻市紫町１番１号 日本たばこ産業株式会社 医薬総合研究所内 Osaka (JP).

(74) 代理人: 高島 一 (TAKASHIMA, Hajime); 〒5410044 大阪府大阪市中央区伏見町四丁目１番１号 明治安田生命大阪御堂筋ビル Osaka (JP).

(81) 指定国 (表示のない限り、全ての種類の国内保護が可能): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) 指定国 (表示のない限り、全ての種類の広域保護が可能): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:
— 国際調査報告書

２文字コード及び他の略語については、定期発行される各*PCT*ガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

DESCRIPTION

HETEROCYCLIC COMPOUND

Technical Field

The present invention relates to heterocyclic compounds, and more particularly, to heterocyclic compounds useful as HSD1 inhibitors.

Background Art

As typically observed in the Cushing's syndrome, excess systemic glucocorticoid effect causes metabolic abnormalities such as accumulation of visceral fat, characteristic changes in body fat distribution, insulin resistance, diabetes, hyperlipidemia, elevation of blood pressure and the like.

It has been known for more than half a century that glucocorticoid plays a key role in diabetes and, for example, removal of hypophysis or adrenal gland from diabetic animal results in the relief of most serious conditions of diabetes and lower blood glucose concentration (see Long, C.D. and F.D.W. Leukins (1936), J. Exp. Med. 63: 465-490 and Houssay, B.A. (1942), Endocrinology, 30: 884-892).

Glucocorticoid is known to (1) be essential for adipocyte differentiation program and inhibit, as a representative insulin-antagonistic hormone, glucose and lipid metabolism by insulin in various steps, (2) raise blood pressure via induction of the production of renin substrate, that is angiotensinogen, enhancement of angiotensin II receptor expression and the like, (3) cause hyperorexia and obesity as a potent leptin antagonistic hormone and the like (see *Rinshoi*, vol. 30 no 9, 2004; 1782-1787).

In addition, it has been drawing attention that abnormally activated glucocorticoid effect in adipose tissue is involved in the pathology of metabolic syndrome clustered multiple metabolic diseases such as diabetes hyperlipidemia, hypertension, fatty liver and the like in a single individual (see Moller DE. New drug targets for 2 diabetes and the metabolic syndrome, Nature 2001; 414: 821-7).

These facts suggest that reduction of the effect of glucocorticoid is beneficial for the treatment or prophylaxis of metabolic diseases such as diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension, fatty liver and the like and metabolic syndrome clustered metabolic diseases in a single individual, and further, fatal vascular events represented by cardiac infarction and cerebral apoplexy based on these diseases.

Active glucocorticoid (cortisol in human and corticosterone in rodents) exhibiting the glucocorticoid effect is produced from cortisone or 11-dehydrocorticosterone, both of which are inactive 11-ketometabolites, by the action of a converting enzyme, 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1), in not only adrenal gland but also various tissues and cells (see Agurwal et al., J. Biol. Chem 264, 18939-46, 1989). Since 11βHSD1 knockout mouse cannot convert an administered inactive glucocorticoid to an active type, this enzyme has been demonstrated to be the only active glucocorticoid converting enzyme in vivo (see Kotelevtsev, Y et al.: Proc. Natl. Acad. Sci. USA, 94: 14924, 1997). There is a report on a case of hypophyseal Cushing's disease with hyperglucocorticoidemia where the conditions of the Cushing's syndrome was not observed due to an markedly lowered 11βHSD1 activity by chance (see Tomlinson, JW et al.: J. Clin. Endocrinol. Metab., 87: 57, 2002).

These results reveal that the regulation of the 11βHSD1 activity is significant for the action of glucocorticoid. In other words, regulation of the 11βHSD1 activity is beneficial for the treatment or prophylaxis of metabolic diseases such as diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension, fatty liver and the like and metabolic syndrome clustered metabolic diseases in a single individual, and further, fatal vascular events represented by cardiac infarction and cerebral apoplexy based on these diseases.

It has been clarified that transgenic mouse, which exhibits overexpression of 11βHSD1, the same level as obese individuals, only in the adipose tissue, also has major factors of metabolic syndromes such as visceral fat-type obesity, insulin-resistant diabetes, hyperlipidemia, hypertension, fatty liver and the like (see Masuzaki, H et al.: Science 2001; 294: 2166-70 and Masuzaki H et al.: J. Clin. Invest 2003; 112: 83-90). In addition, while transgenic mouse exhibiting liver-specific overexpression of 11βHSD1 does not show a phenotype of visceral fat-type obesity but shows insulin resistance and the pathology of hypertension, fatty liver and the like (see Janice M. Paterson et al.: PNAS 2004; 101: 7088-7093). In contrast, 11βHSD1 knockout mouse shows resistance to the induction of hepatic gluconeogenesis enzyme (PEPCK, G6Pase etc.) due to stress-loading or high fat diet-loading, and shows clear resistance to the onset of diabetes (see Kotelevtsev, Y et al.: Proc. Natl. Acad. Sci. USA, 94: 14924, 1997).

Furthermore, 11βHSD1 knockout mouse shows decreased blood triglyceride level and increased blood HDL-cholesterol level, because the expressions of molecular group relating to fat catabolism and their coordinating transcription factor PPARα markedly increased. It has been reported that 11βHSD1 knockout mouse shows clear attenuation of the accumulation of visceral adipose tissue and the onset of metabolic abnormalities induced by high fat diet-loading (see Morton NM et al. J. Biol. Chem. 2001; 44: 41293-301).

In fact, since insulin sensitivity is increased in 11βHSD1 deficiency, inhibition of the effect of this enzyme is expected to be useful for the treatment or prophylaxis of non-insulin dependent diabetes and obesity (see Seckl, JR et al. Eur. J. Biochem. 249: 361, 1997 and Morton NM et al. Diabetes 2004; 53: 931-938).

These findings support that reduction of the effect of 11βHSD1 is beneficial for the treatment or prophylaxis of metabolic diseases such as diabetes, insulin resistance,

diabetic complications, obesity, hyperlipidemia, hypertension, fatty liver and the like and metabolic syndrome clustered metabolic diseases in a single individual, and further, fatal vascular events represented by cardiac infarction and cerebral apoplexy based on those diseases.

Removal of adrenal gland weakens the effect of fasting which increases food intake and expression of hypothalamic neuropeptide Y. This supports the role of glucocorticoid to increase food intake and suggests that inhibition of 11βHSD1 in the brain will increase the satirety level, and therefore, decrease the food intake (see Woods, S.C. et al. (1998) Science, 280:1378-1383). That is, it is suggested that the reduction of the effect of 11βHSD1 is beneficial for the treatment or prophylaxis of hyperorexia.

Stress and glucocorticoids affect the cognitive function (see de Quervain, D.J.-F., B. Roozendaal, and J.L. McGaugh (1998), Nature, 394: 787-790). In fact, 11βHSD1 knockout mouse shows marked improvement in the cognitive dysfunction caused by aging (see Yau J L et al. PNAS 2001; 98: 4716-4721), and a recent report has documented that a 11βHSD1 non-specific inhibitor, carbenoxolone, is effective for cognitive dysfunction of elderly human (see Sandeep T C et al. PNAS 2004; 101: 6734-6739). Furthermore, 11βHSD1 controls the level of action of glucocorticoid in the brain, thereby contributing to the neurotoxicity (see Rajan, V., C.R.W. Edwards, and J.R. Seckl, J. (1996), Neuroscience, 16:65-70 and Seckl, J.R., Front. (2000), Neuroendocrinol, 18:49-99). Moreover, inhibition of 11βHSD1 in the brain results in the reduction of anxiety, which is based on the above-mentioned and known effect of glucocorticoid in the brain (see Tronche, F. et al. (1999), Nature Genetics, 23:99-103). Taken together, therefore, they suggest that the reduction of the 11βHSD1 effect in human brain prevents reactivation of cortisone to cortisol, and is useful for the treatment or prophylaxis of dysgnosia, neurodegenerative diseases accompanied by disappearance of

nerve cells, emotional disorders such as anxiety, depression, mania and the like, schizophrenia, neurodysfunction including appetite stimulation and the like.

It is a well-known fact that glucocorticoid suppresses the immune system. Therefore, reduction of the effect of 11βHSD1 is suggested to be beneficial for the treatment or prophylaxis of diseases showing lowered immunity such as immunodeficiency and the like or for the treatment or prophylaxis of diseases requiring increase of immunity.

Recent data suggest that the levels of glucocorticoid target receptor and 11βHSD1 enzyme determine the susceptibity to glaucoma (see Stokes, J. et al. (2000), Invest. Ophthalmol. 41: 1629-1638). Hence, reduction of the effect of 11βHSD1 is suggested to be beneficial for the treatment or prophylaxis of glaucoma.

Although glucocorticoid plays an essential part in the growth and function of the skeleton, excess glucocorticoid is harmful. Glucocorticoids-induced bone loss is at least partly induced via inhibition of bone formation including suppression of osteoblast growth and collagen synthesis (see Kim, C.H., S.L. Cheng, and G.S. Kim (1999), J. Endocrinol, 162: 371-379).

The negative effect on the bone nodule formation can be blocked by a non-specific 11βHSD1 inhibitor, carbenoxolone, which suggests the important role of 11βHSD1 in the glucocorticoid effect (see Bellows, C.G., A. Ciaccia, and J.N.M. Heersche, (1998), Bone, 23: 119-125). Therefore, reduction of the effect of 11βHSD1 is suggested to be beneficial for the treatment or prophylaxis of osteoporosis.

Accordingly, it can be said that a substance having an activity to reduce the effect of 11βHSD1 is useful as a drug for the treatment or prophylaxis of the pathology involving glucocorticoid, such as

1) metabolic diseases including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension and fatty liver,

2) metabolic syndrome,

3) fatal vascular events represented by cardiac infarction and cerebral apoplexy based on such diseases,

4) hyperorexia,

5) diseases including dysgnosia, neurodegenerative diseases accompanied by disappearance of nerve cells, emotional disorders such as anxiety, depression, mania and the like, schizophrenia and neurodysfunction including appetite stimulation,

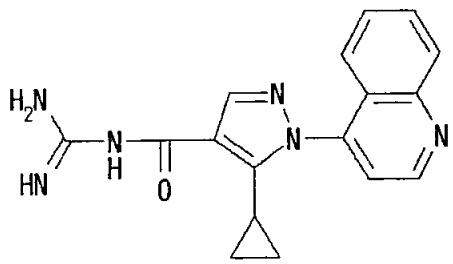
6) diseases requiring treatment or prophylaxis of lowered immunity or increase of immunity, such as immunodeficiency and the like,

7) glaucoma,

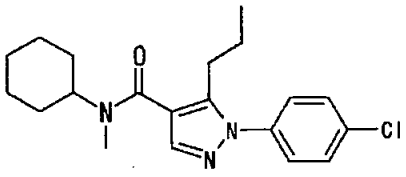
8) osteoporosis

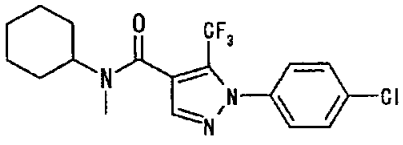
and the like.

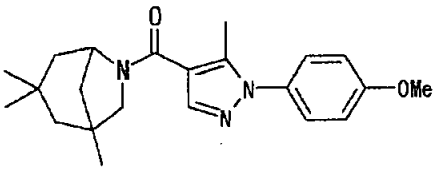
As a heterocyclic compound, for example, the following are known. For example, WO99/43663 discloses the following heterocyclic compound as a compound having am NHE1 inhibitory action.



As known 11βHSD1 inhibitors, for example, the following can be mentioned. WO2004/089470 discloses the following compounds as compounds having an inhibitory action on 11βHSD1:







Disclosure of the Invention

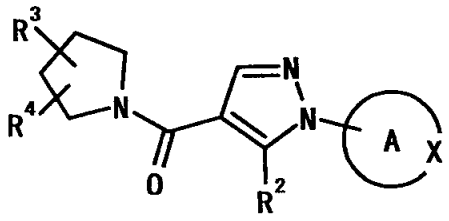
There is a strong demand for the development of a compound useful as an agent for the prophylaxis or treatment of metabolic diseases such as diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension, fatty liver and the like, and the like, and the like, which has more superior properties as a pharmaceutical product in terms of efficacy, duration of action, specificity, low toxicity, oral absorbability, pharmacokinetics and the like.

It is therefore an object of the present invention to provide a compound having an HSD1 inhibitory action and the like and useful as an agent for the prophylaxis or treatment of metabolic diseases such as diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension, fatty liver and the like, and the like, and the like, which has a different chemical structure from that of known compounds including the aforementioned compounds, and use thereof.

The present inventors have first found that a heterocyclic compound mentioned below has a superior HSD1 inhibitory action, and is useful as an agent for the prophylaxis or treatment of metabolic diseases such as diabetes, insulin resistance, diabetic complications, obesity,

hyperlipidemia, hypertension, fatty liver and the like, and the like, and the like. The present inventors have conducted intensive studies based on these findings and completed the present invention. Accordingly, the present invention specifically provides the following.

1. A compound represented by the following formula [1']:



[1']

wherein

ring A is

(1) a nitrogen-containing saturated monocyclic heterocyclic group, or

(2) a cycloalkyl group,

said ring A is optionally substituted by one or more, same or different substituents R^1,

said substituent R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group,

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

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

(h) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or a heterocyclic group which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$

alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally

substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen

atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group, or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a $-COO-C_{1-6}$ alkyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(c) a cycloalkyl group,

(d) a halogen atom,

(e) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a $-COO-C_{1-6}$ alkyl group,

(g) a cyano group, and

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

-X- is

(1) $-N(R^1)-$ wherein R^1 is as defined above, or

(2) $-C(R^7R^8)-$ wherein R^7 and R^8 are the same or different and each is

1) a hydrogen atom,

2) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or $-CO-NR^{36}R^{37}$ wherein R^{36} and R^{37} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{36} and R^{37} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

3) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more carboxyl groups), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, and (b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group, or

5) a carboxyl group;

R^2 is

(1) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a hydroxyl group, and (b) a C_{1-6} alkoxy group), and 2) a C_{1-6} alkoxy group); and

R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, 2) a hydroxyl group, 3) a C_{1-6} alkoxy group, and 4) a $-OCO-C_{1-6}$ alkyl group),

(3) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following 1) to 6):

1) a halogen atom,

2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents

selected from the following group: (a) a halogen atom, (b) a hydroxyl group, and (c) a C_{1-6} alkoxy group),

3) a C_{1-6} alkoxy group (said C_{1-6} alkoxy group is optionally substituted by one or more, same or different halogen atoms),

4) a carboxyl group,

5) a $-COO-C_{1-6}$ alkyl group, and

6) a cyano group),

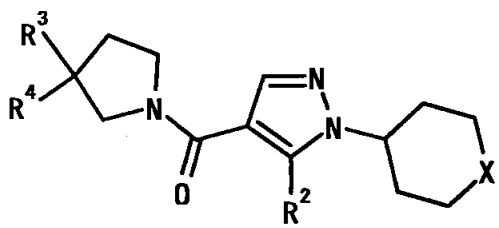
(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

(5) a hydroxyl group, or

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

or a salt thereof.

2. A compound represented by the following formula [1]:



[1]

wherein

-X- is

(1) $-N(R^1)-$ wherein R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group,

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

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

(h) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or a heterocyclic group which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or

different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(c) a nitrogen-containing saturated monocyclic

heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted

by one or more, same or different halogen atoms))),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group, or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic

group is optionally substituted by one or more oxo groups)),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a $-COO-C_{1-6}$ alkyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(c) a cycloalkyl group,

(d) a halogen atom,

(e) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a $-COO-C_{1-6}$ alkyl group,

(g) a cyano group, and

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

(2) $-C(R^7R^8)-$ wherein R^7 and R^8 are the same or different and each is

1) a hydrogen atom,

2) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or $-CO-NR^{36}R^{37}$ wherein R^{36} and R^{37} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{36} and R^{37} optionally

form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

3) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more carboxyl groups), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, and (b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group, or

5) a carboxyl group;

R^2 is

(1) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a hydroxyl group, and (b) a C_{1-6} alkoxy group), and 2) a C_{1-6} alkoxy group); and

R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, 2) a hydroxyl group, 3) a C_{1-6} alkoxy group, and 4) a $-OCO-C_{1-6}$ alkyl group),

(3) an aryl group (said aryl group is optionally substituted by

one or more, same or different substituents selected from the following 1) to 6):

1) a halogen atom,

2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, (b) a hydroxyl group, and (c) a C_{1-6} alkoxy group),

3) a C_{1-6} alkoxy group (said C_{1-6} alkoxy group is optionally substituted by one or more, same or different halogen atoms),

4) a carboxyl group,

5) a $-COO-C_{1-6}$ alkyl group, and

6) a cyano group),

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

(5) a hydroxyl group, or

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

or a salt thereof.

3. The compound of any of the above-mentioned 1 and 2, wherein -X- is $-C(R^7R^8)-$ wherein R^7 and R^8 are as defined in the above-mentioned 1, or a salt thereof.

4. The compound of any of the above-mentioned 1 to 3, wherein R^8 is

1) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

2) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded

thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

3) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group,

or a salt thereof.

5. The compound of the above-mentioned 1 or 2, wherein -X- is $-N(R^1)-$ wherein R^1 is as defined in the above-mentioned 1, or a salt thereof.

6. The compound of any of the above-mentioned 1, 2 and 5, wherein R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group) and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms),

or

(h) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded

thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different -CO-

$NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group), or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a $-COO-C_{1-6}$ alkyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(c) a cycloalkyl group, and

(d) a halogen atom,

(e) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a $-COO-C_{1-6}$ alkyl group,

(g) a cyano group, and

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

or a salt thereof.

7. The compound of any of the above-mentioned 1, 2 and 5, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

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

(h) a nitrogen-containing unsaturated monocyclic

heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not any combination of substituents selected from the following group: (i) a hydrogen atom, and (ii) an unsubstituted C_{1-6} alkyl group),

2) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents

selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from

the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different -CO-$NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

5) a cycloalkyl group,

6) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

7) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

8) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

9) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following (a) to (g):

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(b) a cycloalkyl group,

(c) a halogen atom,

(d) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(e) a $-COO-C_{1-6}$ alkyl group,

(f) a cyano group, and

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

or a salt thereof.

8. The compound of any of the above-mentioned 1, 2 and 5, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a

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

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl

group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group, and

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(h) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the

nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms),

2) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally

substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different -CO-$NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) -CO-$NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

5) a cycloalkyl group,

6) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a

C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

7) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

8) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

9) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following (a) to (g):

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(b) a cycloalkyl group,

(c) a halogen atom,

(d) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(e) a $-COO-C_{1-6}$ alkyl group,

(f) a cyano group, and

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

or a salt thereof.

9. The compound of any of the above-mentioned 1 to 8, wherein R^2 is a cyclopropyl group or a 1-methylcyclopropyl group, or a salt thereof.

10. The compound of any of the above-mentioned 1 to 9, wherein R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a $-OCO-C_{1-6}$ alkyl group),

(3) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following 1) to 5):

1) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, and (b) a hydroxyl group),

2) a C_{1-6} alkoxy group (said C_{1-6} alkoxy group is substituted by one or more, same or different halogen atoms),

3) a carboxyl group,

4) a $-COO-C_{1-6}$ alkyl group, and

5) a cyano group), or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

(provided that R^3 and R^4 are not simultaneously hydrogen atoms),

or a salt thereof.

11. The compound of the above-mentioned 1, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl

group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

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

(h) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms),

2) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group)),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl

group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

5) a cycloalkyl group,

6) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6}

alkyl group is substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

7) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

8) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

9) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group), or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom

bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

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

10) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(c) a cycloalkyl group,

(d) a halogen atom,

(e) -CO-$NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a -COO-C_{1-6} alkyl group,

(g) a cyano group, and

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

or a salt thereof.

12. The compound of the above-mentioned 1, or a salt thereof, which is selected from the following:

(1) 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine,

(2) 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(3) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(4) 1-[1-(1-carbamoylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-

4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(5) 1-{1-[1-(2-carboxyphenylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(6) 1-{5-cyclopropyl-1-[1-(2-hydroxymethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(7) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(8) 1-{5-cyclopropyl-1-[1-(2-hydroxyethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(9) 1-{5-cyclopropyl-1-[1-(2-hydroxy-1,1-dimethylethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(10) 1-{1-[1-(2-acetylaminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(11) 1-{1-[1-(2-aminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(12) 1-{5-cyclopropyl-1-[1-(1,1-dioxothiomorpholine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(13) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(14) 1-{5-cyclopropyl-1-[1-(4-hydroxypiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(15) 1-{1-[1-(azetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(16) 1-{5-cyclopropyl-1-[1-(3-hydroxypyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(17) 1-{5-cyclopropyl-1-[1-(2-piperidin-1-yl-ethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(18) 1-{5-cyclopropyl-1-[1-(4,4-difluoropiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(19) 1-{5-cyclopropyl-1-[1-(3,3-difluoropyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(20) 1-{5-cyclopropyl-1-[1-(3-hydroxyazetidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(21) 1-(5-cyclopropyl-1-{1-[(R)-3-hydroxypyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(22) 1-(5-cyclopropyl-1-{1-[(S)-3-hydroxypyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(23) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxy-1-methylethylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(24) 1-{5-cyclopropyl-1-[1-(4-hydroxymethylpiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(25) 1-{1-[1-(4-carboxypiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(26) 1-{5-cyclopropyl-1-[1-(3-oxopiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(27) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxymethylpyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine,

(28) 1-{5-cyclopropyl-1-[1-(3-hydroxymethylazetidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(29) 1-{5-cyclopropyl-1-[1-(4-methylpiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(30) 1-{5-cyclopropyl-1-[1-(4-isopropylpiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(31) 1-{1-[1-(4-acetylpiperazine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(32) 1-(5-cyclopropyl-1-{1-[(R)-3-hydroxypiperidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(33) 1-{1-[1-(4-carbamoylpiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(34) 1-{1-[1-(3-carbamoylazetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(35) 1-{1-[1-(4-aminopiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(36) 1-{1-[1-(3-aminopyrrolidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(37) 1-{5-cyclopropyl-1-[1-(piperidin-4-yl-carbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(38) 1-{5-cyclopropyl-1-[1-(4-dimethylaminopiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(39) 1-{1-[1-(4-acetylaminopiperidine-1-carbonyl)piperidin-4-

yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(40) 1-{1-[1-(3-acetylaminopyrrolidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(41) 1-{5-cyclopropyl-1-[1-(3-dimethylaminopyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(42) 1-{5-cyclopropyl-1-[1-(1-methylpiperidin-4-yl-carbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(43) 1-{1-[1-(1-acetylpiperidin-4-yl-carbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(44) 1-{5-cyclopropyl-1-[1-(4-oxopiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(45) 1-{1-[1-(3-acetylaminoazetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(46) 1-{5-cyclopropyl-1-[1-(3-oxopyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(47) 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(48) 1-{5-cyclopropyl-1-[1-(3,3,4,4-tetrafluoropyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(49) 1-(5-cyclopropyl-1-{1-[(S)-1-hydroxymethyl-2-methylpropylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(50) 1-(1-{1-[(S)-1-benzyl-2-hydroxyethylcarbamoyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(51) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxy-1-phenylethylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(52) 1-(5-cyclopropyl-1-{1-[(S)-1-hydroxymethyl-3-methylbutylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(53) 1-{5-cyclopropyl-1-[1-(2-hydroxyphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(54) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopentylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(55) 1-[1-(1-benzenesulfonylaminocarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(56) 1-[5-cyclopropyl-1-(1-methanesulfonylaminocarbonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(57) 1-[5-cyclopropyl-1-(1-methoxycarbonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(58) 1-{5-cyclopropyl-1-[1-(2-hydroxyethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(59) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(60) 1-{5-cyclopropyl-1-[1-(2-piperidin-1-yl-ethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(61) 1-{5-cyclopropyl-1-[1-(piperidin-4-yl-oxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(62) 1-{5-cyclopropyl-1-[1-(1-methylpiperidin-4-yl-

oxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(63) 1-{1-[1-(1-acetylpiperidin-4-yl-oxycarbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(64) 1-[1-(1-cyclopropanecarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(65) 1-{5-cyclopropyl-1-[1-(2-hydroxyacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(66) 1-(5-cyclopropyl-1-{1-[1-(4-fluorophenyl)cyclopropanecarbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(67) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(68) 1-{1-[1-(2-acetylaminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(69) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropanecarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(70) 1-{1-[1-(2-acetylamino-2-methylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(71) 1-(1-{1-[(S)-2-acetylaminopropionyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(72) 1-(1-{1-[(S)-2-acetylamino-3-methylbutyryl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(73) 1-{5-cyclopropyl-1-[1-(3,3,3-trifluoropropionyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(74) 1-(5-cyclopropyl-1-{1-[(S)-5-oxopyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(75) 1-{1-[1-(3-acetylaminopropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(76) 1-{5-cyclopropyl-1-[1-(3-hydroxy-2,2-dimethylpropionyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(77) 1-{1-[1-(2-aminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(78) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopropanecarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(79) 1-{1-[1-(2-amino-2-methylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(80) 1-{5-cyclopropyl-1-[1-(4-hydroxybutyryl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(81) 1-(5-cyclopropyl-1-{1-[(S)-pyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(82) 1-(5-cyclopropyl-1-{1-[(S)-1-methylpyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(83) 1-{1-[1-(3-aminopropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(84) 1-(1-{1-[(S)-2-amino-3-methylbutyryl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(85) 1-{5-cyclopropyl-1-[1-(2-methylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine hydrochloride,
(86) 1-{5-cyclopropyl-1-[1-(piperidine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(87) 1-{5-cyclopropyl-1-[1-(2-isobutyrylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(88) 1-{1-[1-(2-cyclopropanecarbonylaminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(89) 1-(1-{1-[(S)-1-acetylpyrrolidine-2-carbonyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(90) 1-{5-cyclopropyl-1-[1-(2-methanesulfonylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(91) 1-{1-[1-(1-acetylpiperidine-4-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(92) 1-{5-cyclopropyl-1-[1-(1-methylpiperidine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(93) 1-{1-[1-(3-carbamoylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(94) 1-[1-(1-carbamoylmethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(95) 1-[5-cyclopropyl-1-(1-methylcarbamoylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(96) 1-{1-[1-(1-carbamoyl-1-methylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(97) 1-{1-[1-(2-carbamoylethyl)piperidin-4-yl]-5-cyclopropyl-

1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(98) 1-[5-cyclopropyl-1-(1-cyclopropylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(99) 1-[5-cyclopropyl-1-(1-cyclopropylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(100) 1-[5-cyclopropyl-1-(1-dimethylcarbamoylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(101) 1-[1-(1-carboxymethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(102) 1-[1-(1-carboxyethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(103) 1-{1-[1-(1-carbamoylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(104) 1-{1-[1-(2-carboxy-2-methylpropyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(105) 1-{1-[1-(2-carbamoyl-2-methylpropyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(106) 1-{1-[1-(1-carbamoylcyclopropylmethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(107) 1-(5-cyclopropyl-1-{1-[1-(2-hydroxyethylcarbamoyl)cyclopropylmethyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(108) 1-[5-cyclopropyl-1-(1-trifluoromethanesulfonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine,

(109) 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethanesulfonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(110) 1-{1-[1-(1-cyanoiminoethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(111) 1-(1-{1-[cyanoimino(methylamino)methyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(112) 1-{1-[1-(N-cyanocarbamimidoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(113)4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid,

(114)3-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid,

(115)5-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiophene-2-carboxylic acid,

(116)2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiazole-4-carboxylic acid,

(117) 1-{5-cyclopropyl-1-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(118) 1-{5-cyclopropyl-1-[1-(5-cyclopropyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(119) 1-{5-cyclopropyl-1-[1-(5-hydroxymethyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(120) 1-{5-cyclopropyl-1-[1-(5-trifluoromethyl-4H-

[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(121) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(122) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(123) 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(124) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(125) 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(126) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(127) (-)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,

(128) (+)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,

(129) 1-[5-cyclopropyl-1-(1-pyrazin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(130) 1-[1-(trans-4-carbamoylcyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(131) 1-[5-cyclopropyl-1-(trans-4-ureidocyclohexyl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(132) 1-{5-cyclopropyl-1-[trans-4-(1H-tetrazol-5-yl)cyclohexyl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(133) 1-{5-(1-methylcyclopropyl)-1-[1-(4-trifluoromethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(134) 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-methoxycyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(135) 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-phenyl-3-trifluoromethyl-pyrrolidine,

(136) 3-(2-chlorophenyl)-1-{5-cyclopropyl-1-[1-(2,4-difluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine,

(137) 3-(2-chloropyridin-3-yl)-1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine,

(138) 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(2,2,3,3-tetramethylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(139) 1-{5-cyclohexyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(140) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethoxyphenyl)pyrrolidine,

(141) 1-{5-cyclopropyl-1-[1-(4-trifluoromethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(142) 1-(5-cyclopropyl-1-{1-[((S)-1-carboxy-2-methyl-propyl)methylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(2-trifluoromethylphenyl)pyrrolidine,

(143) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-methoxy-3-(2-trifluoromethylphenyl)pyrrolidine,

(144) 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-hydroxymethylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(145) 1-{5-cyclopropyl-1-[1-(thiazol-2-ylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(146) 1-{1-[1-(isopropoxycarbamoyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(147) 1-{5-cyclopropyl-1-[1-(4-fluorobenzylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(148) 1-{1-[1-(2,3-dihydroindole-1-carbonyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(149) 1-{1-[1-(2,3-dihydro[1,4]oxazine-4-carbonyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(150) 1-{5-cyclopropyl-1-[1-(2,6-dichloropyridin-3-ylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(151) 1-{5-(1-methylcyclopropyl)-1-[1-(2,3,4,5-tetrahydrobenzo[b]azepine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(152) ethyl 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoate,

(153) 1-[1-(1-benzyloxycarbonyl-piperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine,

(154) 1-{1-[1-(3-carboxy-3-methyl-butyryl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(155) 1-{5-cyclopropyl-1-[1-(2-phenoxyacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(156) 1-{1-[1-(3-chlorobenzoyl)piperidin-4-yl]-5-cyclopropyl-

1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,
(157) 1-{1-[1-(2-chlorobenzoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,
(158) 1-[5-cyclopropyl-1-(1-oxalylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine,
(159) 1-{1-[1-(4-chlorobenzoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,
(160) 1-(5-cyclopropyl-1-{1-[2-(4-fluorophenyl)acetyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(pyridin-3-yl)pyrrolidine,
(161) 1-{5-cyclopropyl-1-[1-(3-trifluoromethylbenzoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,
(162) 1-{5-cyclopropyl-1-[1-(3-methoxybenzoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,
(163) 1-{1-[1-(4-fluorobenzyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine hydrochloride,
(164) 1-[1-(1-benzenesulfonyl-piperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine,
(165) 1-{1-[1-(4-carbamoylphenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,
(166) 1-{5-cyclopropyl-1-[1-(4-hydroxymethylphenyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,
(167) 1-{1-[1-(5-carbamoyl-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,
(168) 1-{1-[1-(4-aminophenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,
(169) 1-(5-cyclopropyl-1-{1-[4-(2-oxooxazolidin-3-yl)phenyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(2-trifluoromethylphenyl)pyrrolidine,
(170) 1-(5-cyclopropyl-1-{1-[4-(3-methoxyureido)phenyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-

(2-trifluoromethylphenyl)pyrrolidine,

(171) 1-{5-cyclopropyl-1-[1-(4-methanesulfonylaminophenyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(172) 1-[1-(1-ethoxycarbamoylpiperidin-4-yl)-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine,

(173) 1-[1-(5-chloropyridin-2-yl)azetidin-3-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine,

(174) 1-{1-[1-(5-chloro-pyridin-2-yl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-methoxymethyl-3-phenylpyrrolidine,

(175) 1-{1-[1-(5-cyano-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(176) 3-(2-acetoxyethyl)-3-(4-fluorophenyl)-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,

(177) {(3S*,4R*)-3-methyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-4-phenylpyrrolidine hydrochloride,

(178) methyl 6-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)nicotinate,

(179) methyl 2-{1-[5-(1-methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]pyrrolidin-3-yl}benzoate,

(180) 3-(2-hydroxymethylphenyl)-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,

(181) 1-[5-cyclopropyl-1-(1-pyridin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-hydroxy-3-(pyridin-3-yl)pyrrolidine,

(182) 1-{1-[1-(4-acetylaminophenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(183) sodium 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)-3-fluorobenzoate,

(184) 3-(2-cyanophenyl)-1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine,

(185) 3-hydroxymethyl-1-{1-[1-(4-methoxypyrimidin-2-yl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-phenylpyrrolidine hydrochloride,

(186) 3-(3,5-difluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,

(187) 1-{1-[1-(3-chloro-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(188) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(thiazol-2-yl)pyrrolidine,

(189) (S)-2-[(trans-4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)-pyrrolidine-1-carbonyl]-pyrazol-1-yl}-cyclohexanecarbonyl)-methyl-amino]-3-methylbutyric acid,

(190) 1-{5-(1-methylcyclopropyl)-1-[trans-4-(2-fluorophenylcarbamoyl)cyclohexyl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine, and

(191) cis-4-{5-(1-methylcyclopropyl)-4-[3-(2-trifluoromethylphenyl)-pyrrolidine-1-carbonyl]-pyrazol-1-yl)-cyclohexanecarboxylic acid.

13. A pharmaceutical composition comprising a compound of any of the above-mentioned 1 to 12 or a salt thereof.

14. A 11βHSD1 inhibitor comprising a compound of any of the above-mentioned 1 to 12 or a salt thereof.

15. An agent for the treatment or prophylaxis of a pathology involving glucocorticoid, which comprises a compound of any of the above-mentioned 1 to 12 or a salt thereof.

16. The agent of the above-mentioned 15, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis.

17. A method of inhibiting 11βHSD1, which comprises administering a pharmaceutically effective amount of a compound of any of the above-mentioned 1 to 12 or a salt thereof.

18. A method of treating or preventing a pathology involving glucocorticoid, which comprises administering a pharmaceutically effective amount of a compound of any of the above-mentioned 1 to 12 or a salt thereof.

19. The method of the above-mentioned 18, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis.

20. Use of a compound of any of the above-mentioned 1 to 12 or a salt thereof for the production of a 11βHSD1 inhibitor.

21. Use of a compound of any of the above-mentioned 1 to 12 or a salt thereof for the production of an agent for the treatment or prophylaxis of a pathology involving glucocorticoid.

22. Use of the above-mentioned 21, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis.

23. A commercial package comprising a written matter stating that the pharmaceutical composition of the above-mentioned 13 can or should be used for the treatment or prophylaxis of a disease selected from

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis.

24. The pharmaceutical composition of the above-mentioned 13 to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

25. The 11βHSD1 inhibitor of the above-mentioned 14, to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

26. The agent of the above-mentioned 15 or 16, which is to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

27. The method of the above-mentioned 17, further comprising administering 1 to 3 agents selected from the

following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

28. A pharmaceutical agent comprising 1 to 3 agents selected from the following (1) to (5) and a compound of any of the above-mentioned 1 to 12 or a salt thereof in combination:

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

29. A method of treating or preventing the pathology involving glucocorticoid of the above-mentioned 18 or 19, which further comprises administering 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

30. The use of the above-mentioned 20, which is to be combined with the use of 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

31. The use of the above-mentioned 21 or 22, which is to be combined with the use of 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

32. The pharmaceutical composition of the above-mentioned 13, which is used for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

33. The 11βHSD1 inhibitor of the above-mentioned 14, which is used for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

34. The method of the above-mentioned 17, which further comprises administering a pharmaceutical agent raising the blood glucocorticoid level.

35. The use of the above-mentioned 21 for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

36. A method for suppressing the blood glucocorticoid level from rising, which comprises administering a pharmaceutical agent raising the blood glucocorticoid level and the 11βHSD1 inhibitor of the above-mentioned 14.

37. Dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate.

38. Methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate.

39. (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one.

40. (S)-3-(2-trifluoromethylphenyl)pyrrolidine or a salt thereof.

41. A method for producing dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate, which comprises a step for reacting 1-((E)-2-nitrovinyl)-2-trifluoromethylbenzene with dimethyl malonate in the presence of 1-(3,5-bis-trifluoromethylphenyl)-3-((1S,2S)-2-dimethylaminocyclohexyl)-thiourea.

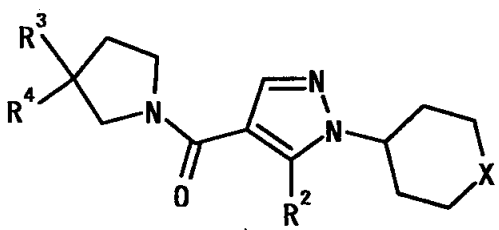
42. A method for producing methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate, which comprises a step for reduction and ring closure of dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate.

43. A method for producing (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one, which comprises a step for hydrolysis and decarbonation of methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate.

44. A method for producing a salt of (S)-3-(2-trifluoromethylphenyl)pyrrolidine, which comprises a step for reducing (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one and a step for treating the resulting compound with an acid to form a salt.

The present invention also encompasses the following.

45. A compound represented by the following formula [2]:



[2]

wherein

-X- is

(1) $-N(R^1)-$ wherein R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated

monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or a heterocyclic group which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

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

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents

selected from the following a) to g):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

g) a carboxyl group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different

substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group), or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a $-COO-C_{1-6}$ alkyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (g):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(c) a cycloalkyl group,

(d) a halogen atom,

(e) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a $-COO-C_{1-6}$ alkyl group, and

(g) a cyano group), or

(2) $-C(R^7R^8)-$ wherein R^7 and R^8 are the same or different and each is

1) a hydrogen atom,

2) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or $-CO-NR^{36}R^{37}$ wherein R^{36} and R^{37} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{36} and R^{37} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

3) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl

group is optionally substituted by one or more carboxyl groups), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, and (b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group, or

5) a carboxyl group;

R^2 is

(1) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a hydroxyl group, and (b) a C_{1-6} alkoxy group)); and

R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, 2) a hydroxyl group, and 3) a C_{1-6} alkoxy group),

(3) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following 1) to 6):

1) a halogen atom,

2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, (b) a hydroxyl group, and (c) a C_{1-6} alkoxy group),

3) a C_{1-6} alkoxy group (said C_{1-6} alkoxy group is optionally substituted by one or more, same or different halogen atoms),

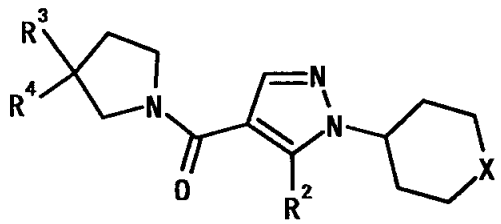
4) a carboxyl group,

5) a -COO-C_{1-6} alkyl group, and

6) a cyano group), or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a salt thereof.

46. The compound of the above-mentioned 45, which is represented by the following formula [2]:



[2]

wherein

-X- is

(1) -N(R^1)- wherein R^1 is

1) a hydrogen atom,

2) -CONR^{5}R^6 wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group),

3) $-COOR^{10}$ wherein R^{10} is,

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents

selected from the following a) to c):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

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

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is,

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to e):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

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

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different

substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (c):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group), and

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom

bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a carboxyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (c):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(c) a cycloalkyl group), or

(2) $-C(R^7R^8)-$ wherein R^7 and R^8 are the same or different and each is

1) a hydrogen atom,

2) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or $-CO-NR^{36}R^{37}$

wherein R^{36} and R^{37} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{36} and R^{37} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

3) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group;

R^2 is

(1) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups); and

R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

(3) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following 1) and 2):

1) a halogen atom, and

2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group,

or a salt thereof.

47. The compound of the above-mentioned 45 or 46, wherein

-X- is $-C(R^7R^8)-$ wherein R^7 and R^8 are as defined in the above-mentioned 46, or a salt thereof.

48. The compound of any of the above-mentioned 45 to 47, wherein R^8 is

1) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

2) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

3) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group),

or a salt thereof.

49. The compound of the above-mentioned 45 or 46, wherein -X- is $-N(R^1)-$ wherein R^1 is as defined in the above-mentioned 46), or a salt thereof.

50. The compound of any of the above-mentioned 45, 46 and 49, wherein R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a

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

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or

different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

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

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to e):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

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

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (c):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group), and

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or

different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a carboxyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (c):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(c) a cycloalkyl group),

or a salt thereof.

51. The compound of any of the above-mentioned 45, 46 and 49, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is

optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or

R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms and unsubstituted C_{1-6} alkyl groups),

2) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

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

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to e):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

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

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from

the following (a) to (c):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group), and

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

5) a cycloalkyl group,

6) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different halogen atoms),

7) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

8) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

9) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following (a) and (b):

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(b) a cycloalkyl group),

or a salt thereof.

52. The compound of any of the above-mentioned 45, 46 and 49, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally

substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents

selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms and unsubstituted C_{1-6} alkyl groups),

2) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

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

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to e):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

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

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents

selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following (a) to (c):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group), and

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

5) a cycloalkyl group,

6) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different halogen atoms),

7) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

8) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

9) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by

one or more, same or different substituents selected from the following (a) and (b):

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(b) a cycloalkyl group),

or a salt thereof.

53. The compound of any of the above-mentioned 45 to 52, wherein R^2 is a cyclopropyl group or a 1-methylcyclopropyl group, or a salt thereof.

54. The compound of any of the above-mentioned 45 to 53, wherein R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

(3) a phenyl group (said phenyl group is optionally substituted by one or more, same or different substituents selected from the following 1) and 2):

1) a halogen atom, and

2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group,

or a salt thereof.

55. The compound of the above-mentioned 45 or a salt thereof, which is selected from the following:

(1) 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine,

(2) 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-

carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(3) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(4) 1-[1-(1-carbamoylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(5) 1-{1-[1-(2-carboxyphenylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(6) 1-{5-cyclopropyl-1-[1-(2-hydroxymethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(7) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(8) 1-{5-cyclopropyl-1-[1-(2-hydroxyethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(9) 1-{5-cyclopropyl-1-[1-(2-hydroxy-1,1-dimethylethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(10) 1-{1-[1-(2-acetylaminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(11) 1-{1-[1-(2-aminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(12) 1-{5-cyclopropyl-1-[1-(1,1-dioxothiomorpholine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(13) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(14) 1-{5-cyclopropyl-1-[1-(4-hydroxypiperidine-1-

carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(15) 1-{1-[1-(azetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(16) 1-{5-cyclopropyl-1-[1-(3-hydroxypyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(17) 1-{5-cyclopropyl-1-[1-(2-piperidin-1-yl-ethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(18) 1-{5-cyclopropyl-1-[1-(4,4-difluoropiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(19) 1-{5-cyclopropyl-1-[1-(3,3-difluoropyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(20) 1-{5-cyclopropyl-1-[1-(3-hydroxyazetidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(21) 1-(5-cyclopropyl-1-{1-[(R)-3-hydroxypyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(22) 1-(5-cyclopropyl-1-{1-[(S)-3-hydroxypyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(23) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxy-1-methylethylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(24) 1-{5-cyclopropyl-1-[1-(4-hydroxymethylpiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(25) 1-{1-[1-(4-carboxypiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(26) 1-{5-cyclopropyl-1-[1-(3-oxopiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(27) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxymethylpyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(28) 1-{5-cyclopropyl-1-[1-(3-hydroxymethylazetidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(29) 1-{5-cyclopropyl-1-[1-(4-methylpiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(30) 1-{5-cyclopropyl-1-[1-(4-isopropylpiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(31) 1-{1-[1-(4-acetylpiperazine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(32) 1-(5-cyclopropyl-1-{1-[(R)-3-hydroxypiperidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(33) 1-{1-[1-(4-carbamoylpiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(34) 1-{1-[1-(3-carbamoylazetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(35) 1-{1-[1-(4-aminopiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(36) 1-{1-[1-(3-aminopyrrolidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(37) 1-{5-cyclopropyl-1-[1-(piperidin-4-yl-carbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine hydrochloride,

(38) 1-{5-cyclopropyl-1-[1-(4-dimethylaminopiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(39) 1-{1-[1-(4-acetylaminopiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(40) 1-{1-[1-(3-acetylaminopyrrolidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(41) 1-{5-cyclopropyl-1-[1-(3-dimethylaminopyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(42) 1-{5-cyclopropyl-1-[1-(1-methylpiperidin-4-yl-carbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(43) 1-{1-[1-(1-acetylpiperidin-4-yl-carbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(44) 1-{5-cyclopropyl-1-[1-(4-oxopiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(45) 1-{1-[1-(3-acetylaminoazetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(46) 1-{5-cyclopropyl-1-[1-(3-oxopyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(47) 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(48) 1-{5-cyclopropyl-1-[1-(3,3,4,4-tetrafluoropyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(49) 1-(5-cyclopropyl-1-{1-[(S)-1-hydroxymethyl-2-

methylpropylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(50) 1-(1-{1-[(S)-1-benzyl-2-hydroxyethylcarbamoyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(51) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxy-1-phenylethylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(52) 1-(5-cyclopropyl-1-{1-[(S)-1-hydroxymethyl-3-methylbutylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(53) 1-{5-cyclopropyl-1-[1-(2-hydroxyphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(54) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopentylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(55) 1-[1-(1-benzenesulfonylaminocarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(56) 1-[5-cyclopropyl-1-(1-methanesulfonylaminocarbonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(57) 1-[5-cyclopropyl-1-(1-methoxycarbonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(58) 1-{5-cyclopropyl-1-[1-(2-hydroxyethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(59) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(60) 1-{5-cyclopropyl-1-[1-(2-piperidin-1-yl-ethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-

(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(61) 1-{5-cyclopropyl-1-[1-(piperidin-4-yl-oxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(62) 1-{5-cyclopropyl-1-[1-(1-methylpiperidin-4-yl-oxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(63) 1-{1-[1-(1-acetylpiperidin-4-yl-oxycarbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(64) 1-[1-(1-cyclopropanecarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(65) 1-{5-cyclopropyl-1-[1-(2-hydroxyacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(66) 1-(5-cyclopropyl-1-{1-[1-(4-fluorophenyl)cyclopropanecarbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(67) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(68) 1-{1-[1-(2-acetylaminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(69) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropanecarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(70) 1-{1-[1-(2-acetylamino-2-methylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(71) 1-(1-{1-[(S)-2-acetylaminopropionyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(72) 1-(1-{1-[(S)-2-acetylamino-3-methylbutyryl]piperidin-4-

yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(73) 1-{5-cyclopropyl-1-[1-(3,3,3-trifluoropropionyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(74) 1-(5-cyclopropyl-1-{1-[(S)-5-oxopyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(75) 1-{1-[1-(3-acetylaminopropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(76) 1-{5-cyclopropyl-1-[1-(3-hydroxy-2,2-dimethylpropionyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(77) 1-{1-[1-(2-aminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(78) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopropanecarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(79) 1-{1-[1-(2-amino-2-methylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(80) 1-{5-cyclopropyl-1-[1-(4-hydroxybutyryl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(81) 1-(5-cyclopropyl-1-{1-[(S)-pyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(82) 1-(5-cyclopropyl-1-{1-[(S)-1-methylpyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(83) 1-{1-[1-(3-aminopropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(84) 1-(1-{1-[(S)-2-amino-3-methylbutyryl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(85) 1-{5-cyclopropyl-1-[1-(2-methylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(86) 1-{5-cyclopropyl-1-[1-(piperidine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(87) 1-{5-cyclopropyl-1-[1-(2-isobutyrylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(88) 1-{1-[1-(2-cyclopropanecarbonylaminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(89) 1-(1-{1-[(S)-1-acetylpyrrolidine-2-carbonyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(90) 1-{5-cyclopropyl-1-[1-(2-methanesulfonylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(91) 1-{1-[1-(1-acetylpiperidine-4-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(92) 1-{5-cyclopropyl-1-[1-(1-methylpiperidine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(93) 1-{1-[1-(3-carbamoylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(94) 1-[1-(1-carbamoylmethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(95) 1-[5-cyclopropyl-1-(1-methylcarbamoylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine hydrochloride,
(96) 1-{1-[1-(1-carbamoyl-1-methylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(97) 1-{1-[1-(2-carbamoylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(98) 1-[5-cyclopropyl-1-(1-cyclopropylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(99) 1-[5-cyclopropyl-1-(1-cyclopropylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(100) 1-[5-cyclopropyl-1-(1-dimethylcarbamoylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(101) 1-[1-(1-carboxymethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(102) 1-[1-(1-carboxyethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(103) 1-{1-[1-(1-carbamoylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(104) 1-{1-[1-(2-carboxy-2-methylpropyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(105) 1-{1-[1-(2-carbamoyl-2-methylpropyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(106) 1-{1-[1-(1-carbamoylcyclopropylmethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(107) 1-(5-cyclopropyl-1-{1-[1-(2-

hydroxyethylcarbamoyl)cyclopropylmethyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(108) 1-[5-cyclopropyl-1-(1-trifluoromethanesulfonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(109) 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethanesulfonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(110) 1-{1-[1-(1-cyanoiminoethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(111) 1-(1-{1-[cyanoimino(methylamino)methyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(112) 1-{1-[1-(N-cyanocarbamimidoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(113) 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid,

(114) 3-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid,

(115) 5-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiophene-2-carboxylic acid,

(116) 2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiazole-4-carboxylic acid,

(117) 1-{5-cyclopropyl-1-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(118) 1-{5-cyclopropyl-1-[1-(5-cyclopropyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine hydrochloride,
(119) 1-{5-cyclopropyl-1-[1-(5-hydroxymethyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(120) 1-{5-cyclopropyl-1-[1-(5-trifluoromethyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(121) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(122) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(123) 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(124) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(125) 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(126) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(127) (-)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,
(128) (+)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,
(129) 1-[5-cyclopropyl-1-(1-pyrazin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(130) 1-[1-(trans-4-carbamoylcyclohexyl)-5-cyclopropyl-1H-

pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(131) 1-[5-cyclopropyl-1-(trans-4-ureidocyclohexyl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine, and

(132) 1-{5-cyclopropyl-1-[trans-4-(1H-tetrazol-5-yl)cyclohexyl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine.

56. A pharmaceutical composition comprising a compound of any of the above-mentioned 45 to 55 or a salt thereof.

57. A 11βHSD1 inhibitor comprising a compound of any of the above-mentioned 45 to 55 or a salt thereof.

58. An agent for the treatment or prophylaxis of a pathology involving glucocorticoid, which comprises a compound of any of the above-mentioned 45 to 55 or a salt thereof.

59. The agent of the above-mentioned 58, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy based on such diseases,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases accompanied by disappearance of nerve cells, emotional disorders including anxiety, depression or mania, schizophrenia or appetite stimulation,

(6) a disease requiring treatment or prophylaxis of lowered immunity or increase of immunity, including immunodeficiency,

(7) glaucoma, or

(8) osteoporosis.

60. A method of inhibiting 11βHSD1, which comprises administering a pharmaceutically effective amount of a compound of any of the above-mentioned 45 to 55 or a salt thereof.

61. A method of treating or preventing a pathology involving glucocorticoid, which comprises administering a pharmaceutically effective amount of a compound of any of the above-mentioned 45 to 55 or a salt thereof.

62. The method of the above-mentioned 61, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy based on such diseases,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases accompanied by disappearance of nerve cells, emotional disorders including anxiety, depression or mania, schizophrenia or appetite stimulation,

(6) a disease requiring treatment or prophylaxis of lowered immunity or increase of immunity, including immunodeficiency,

(7) glaucoma, or

(8) osteoporosis.

63. Use of a compound of any of the above-mentioned 45 to 55 or a salt thereof for the production of a 11βHSD1 inhibitor.

64. Use of a compound of any of the above-mentioned 45 to 55 or a salt thereof for the production of an agent for the treatment or prophylaxis of a pathology involving glucocorticoid.

65. Use of the above-mentioned 64, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or

cerebral apoplexy based on such diseases,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases accompanied by disappearance of nerve cells, emotional disorders including anxiety, depression or mania, schizophrenia or appetite stimulation,

(6) a disease requiring treatment or prophylaxis of lowered immunity or increase of immunity, including immunodeficiency,

(7) glaucoma, or

(8) osteoporosis.

66. A commercial package comprising a written matter stating that the pharmaceutical composition of the above-mentioned 56 can or should be used for the treatment or prophylaxis of a disease selected from

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy based on such diseases,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases accompanied by disappearance of nerve cells, emotional disorders including anxiety, depression or mania, schizophrenia or appetite stimulation,

(6) a disease requiring treatment or prophylaxis of lowered immunity or increase of immunity, including immunodeficiency,

(7) glaucoma, and

(8) osteoporosis.

67. The pharmaceutical composition of the above-mentioned 56 to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

68. The 11βHSD1 inhibitor of the above-mentioned 57, to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

69. The agent of the above-mentioned 58 or 59, which is to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

70. The method of the above-mentioned 60, further comprising administering 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

71. A pharmaceutical agent comprising 1 to 3 agents

selected from the following (1) to (5) and a compound of any of the above-mentioned 45 to 55 or a salt thereof in combination:

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

72. A method of treating or preventing the pathology involving glucocorticoid of the above-mentioned 61 or 62, which further comprises administering 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

73. The use of the above-mentioned 63, which is to be combined with the use of 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

74. The use of the above-mentioned 64 or 65, which is to be combined with the use of 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

75. The pharmaceutical composition of the above-mentioned 56, which is used for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

76. The 11βHSD1 inhibitor of the above-mentioned 57, which is used for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

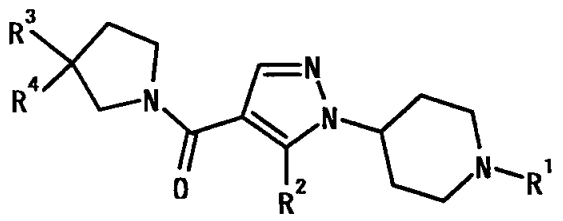
77. The method of the above-mentioned 60, which further comprises administering a pharmaceutical agent raising the blood glucocorticoid level.

78. The use of the above-mentioned 64 for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

79. A method for suppressing the blood glucocorticoid level from rising, which comprises administering a pharmaceutical agent raising the blood glucocorticoid level and the 11βHSD1 inhibitor of the above-mentioned 57.

The present invention further comprises the following.

80. A compound represented by the following formula [3]:



[3]

wherein

R^1 is

(1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and

each is

1) a hydrogen atom,

2) a C_{1-6} alkyl group,

3) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups), or

4) an aryl group (said aryl group is optionally substituted by one or more, same or different halogen atoms),

(2) an aryl group (said aryl group is optionally substituted by one or more carboxyl groups), or

(3) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more carboxyl groups);

R^2 is

(1) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups); and

R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more hydroxyl groups),

(3) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from a halogen atom and a C_{1-6} alkyl group optionally substituted by one or more halogen atoms), or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group,

or a pharmaceutically acceptable salt thereof.

81. The compound of the above-mentioned 80, wherein R^1 is

(1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

1) a hydrogen atom,

2) a C_{1-6} alkyl group,

3) a cyclopropyl group (said cyclopropyl group is optionally substituted by one or more, same or different C_{1-6}

alkyl groups), or

4) a phenyl group (said phenyl group is optionally substituted by one or more, same or different halogen atoms),

(2) a phenyl group (said phenyl group is optionally substituted by one or more carboxyl groups), or

(3) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more carboxyl groups), or a pharmaceutically acceptable salt thereof.

82. The compound of the above-mentioned 80, wherein R^2 is a cyclopropyl group or a methylcyclopropyl group, or a pharmaceutically acceptable salt thereof.

83. The compound of the above-mentioned 80, wherein R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more hydroxyl groups),

(3) a phenyl group (said phenyl group is optionally substituted by one or more, same or different substituents selected from a halogen atom and a C_{1-6} alkyl group optionally substituted by one or more halogen atoms), or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group, or a pharmaceutically acceptable salt thereof.

84. The compound of the above-mentioned 80 or a pharmaceutically acceptable salt thereof, which is selected from the following:

(1) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-(3-pyridin-3-yl)pyrrolidine,

(2) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{(R)-3-(2-trifluoromethylphenyl)}pyrrolidine,

(3) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{(R)-3-(2-trifluoromethylphenyl)}pyrrolidine,

(4) 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{(R)-3-(2-trifluoromethylphenyl)}pyrrolidine,

(5) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{(S)-3-(2-trifluoromethylphenyl)}pyrrolidine,

(6) 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{(S)-3-(2-trifluoromethylphenyl)}pyrrolidine,

(7) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{(S)-3-(2-trifluoromethylphenyl)}pyrrolidine,

(8) (-)1-{5-(1-methylcyclopropyl)-1-[(1-pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine hydrochloride,

(9) (+)1-{5-(1-methylcyclopropyl)-1-[(1-pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine hydrochloride,

(10) 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid,

(11) 3-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid,

(12) 5-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiophene-2-carboxylic acid, and

(13) 2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiazole-4-carboxylic acid.

85. A pharmaceutical composition comprising the compound of any of the above-mentioned 80 to 84, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

86. A 11βHSD1 inhibitor comprising the compound of any of

the above-mentioned 80 to 84, or a pharmaceutically acceptable salt thereof, as an active ingredient.

87. An agent for the treatment or prophylaxis of a pathology involving glucocorticoid, which comprises the compound of any of the above-mentioned 80 to 84, or a pharmaceutically acceptable salt thereof, as an active ingredient.

88. The agent of the above-mentioned 87, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy based on such diseases,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases accompanied by disappearance of nerve cells, emotional disorders including anxiety, depression or mania, schizophrenia or appetite stimulation,

(6) a disease requiring treatment or prophylaxis of lowered immunity or increase of immunity, including immunodeficiency,

(7) glaucoma, or

(8) osteoporosis.

89. The pharmaceutical composition of the above-mentioned 85 to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

90. The 11βHSD1 inhibitor of the above-mentioned 86, to

be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

91. The agent of the above-mentioned 87 or 88, which is to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

92. The pharmaceutical composition of the above-mentioned 85, which is used for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

93. The 11βHSD1 inhibitor of the above-mentioned 86, which is used for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

Best Mode for Embodying the Invention

The present invention is described in detail in the following.

In the present invention, the definitions of the substituents to be used are as follows.

The "C_{1-6} alkyl group" is a linear or branched chain alkyl group having 1 to 6 carbon atoms and, for example, methyl group, ethyl group, propyl group, isopropyl group, butyl group,

isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, tert-pentyl group, 1,2-dimethyl-propyl group, hexyl group, 1,3-dimethyl-butyl group and the like can be mentioned, with preference given to a linear or branched chain alkyl group having 1 to 4 carbon atoms.

For R^1, preferable "C_{1-6} alkyl group" is methyl group, ethyl group, isopropyl group or isobutyl group.

For R^3 or R^4, preferable "C_{1-6} alkyl group" is methyl group.

For R^5 or R^6, preferable "C_{1-6} alkyl group" is ethyl group, isopropyl group, tert-butyl group, 1,2-dimethyl-propyl group or 1,3-dimethyl-butyl group.

For R^9, preferable "C_{1-6} alkyl group" is methyl group.

For R^{10}, preferable "C_{1-6} alkyl group" is methyl group or ethyl group.

For R^{11}, preferable "C_{1-6} alkyl group" is methyl group, ethyl group, propyl group, isopropyl group, isobutyl group or tert-butyl group.

For R^{12}, preferable "C_{1-6} alkyl group" is methyl group or ethyl group.

For R^{13}, preferable "C_{1-6} alkyl group" is methyl group.

For R^{14} or R^{15}, preferable "C_{1-6} alkyl group" is methyl group.

The "C_{2-6}alkenyl group" is a linear or branched chain alkenyl group having 2 to 6 carbon atoms and, for example, vinyl group, n-propenyl group, isopropenyl group, n-butenyl group, isobutenyl group, sec-butenyl group, tert-butenyl group, n-pentenyl group, isopentenyl group, neopentenyl group, 1-methylpropenyl group, n-hexenyl group, isohexenyl group, 1,1-dimethylbutenyl group, 2,2-dimethylbutenyl group, 3,3-dimethylbutenyl group, 3,3-dimethylpropenyl group, 2-ethylbutenyl group and the like can be mentioned.

The "C_{1-6} alkoxy group" is an alkoxy group wherein the alkyl moiety is the "C_{1-6} alkyl group" defined above and, for

example, methoxy group, ethoxy group, propoxy group, isopropyloxy group, butoxy group, isobutyloxy group, tert-butyloxy group, pentyloxy group, hexyloxy group and the like can be mentioned.

The "halogen atom" is fluorine atom, chlorine atom, bromine atom or iodine atom. Preferred is fluorine atom or chlorine atom and more preferred is fluorine atom.

The "aryl group" is an aromatic hydrocarbon group having 6 to 14 carbon atoms and, for example, phenyl group, naphthyl group, anthryl group, azulenyl group, phenanthryl group and the like can be mentioned. Preferred is phenyl group.

The "aryloxy group" is an aryloxy group wherein the aryl moiety is the "aryl group" defined above and, for example, phenoxy group, naphthyloxy group and the like can be mentioned.

The "cycloalkyl group" is a cycloalkyl group having 3 to 8 carbon atoms and, for example, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group and the like can be mentioned. Preferred is cycloalkyl group having 3 to 6 carbon atoms, such as cyclopropyl group, cyclobutyl group, cyclopentyl group and cyclohexyl group. Particularly preferred is cyclopropyl group and cyclopentyl group.

The "5-membered or 6-membered unsaturated monocyclic heterocyclic group" is a 5-membered or 6-membered unsaturated monocyclic heterocyclic group having, besides carbon atom, at least one, preferably 1 to 4, hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom. The unsaturated includes partial unsaturation and complete unsaturation. For example, a 5-membered monocyclic aromatic heterocyclic group such as furyl group, thienyl group, pyrrolyl group, pyrazolyl group, imidazolyl group, oxazolyl group, isoxazolyl group, thiazolyl group, isothiazolyl group, triazolyl group, oxadiazolyl group, tetrazolyl group, thiadiazolyl group and the like, and a 6-membered monocyclic aromatic heterocyclic group

such as pyridyl group, pyridazinyl group, pyrimidinyl group, pyrazinyl group, triazinyl group, thiazinyl group, oxadiazinyl group, pyranyl group, thiopyranyl group and the like can be mentioned. As the 5-membered monocyclic aromatic heterocyclic group, preferred is thienyl group or thiazolyl group. As the 6-membered monocyclic aromatic heterocyclic group, preferred is pyridyl group or pyrimidinyl group.

For R^1, preferable "5-membered or 6-membered unsaturated monocyclic heterocyclic group" is pyridyl group, thienyl group, thiazolyl group, triazolyl group (particularly preferably 1,2,4-triazolyl group), tetrazolyl group, pyrimidinyl group or pyrazinyl group.

For R^3 or R^4, preferable "5-membered or 6-membered unsaturated monocyclic heterocyclic group" is pyridyl group or thiazolyl group. More preferred is pyridyl group.

The "nitrogen-containing saturated monocyclic heterocyclic group" is, for example, a 4-membered to 6-membered saturated monocyclic heterocycle having at least one nitrogen atom, such as azetidinyl group, pyrrolidinyl group, imidazolidinyl group, pyrazolidinyl group, oxazolidinyl group, 2-oxopyrrolidinyl group, thiazolidinyl group, isothiazolidinyl group, piperidyl group, piperazinyl group, morpholinyl group, thiomorpholinyl group, 2-oxopiperidinyl group, 4-oxopiperidinyl group, 2,6-dioxopiperidinyl group and the like.
preferable "nitrogen-containing saturated monocyclic heterocyclic group" is azetidinyl group, pyrrolidinyl group, piperidyl group, piperazinyl group or thiomorpholinyl group.

For $-NR^5R^6$, preferable "nitrogen-containing saturated monocyclic heterocyclic group" is azetidinyl group, pyrrolidinyl group, piperidyl group, piperazinyl group or thiomorpholinyl group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following group:
halogen atom,
hydroxyl group,

C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups,
carboxyl group,
acetyl group,
carbamoyl group,
amino group optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and acetyl group, and
oxo group).

For $-NR^{20}R^{21}$, preferable "nitrogen-containing saturated monocyclic heterocyclic group" is azetidinyl group, pyrrolidinyl group or piperidyl group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from halogen atom and hydroxyl group).

For $-NR^{26}R^{27}$, preferable "nitrogen-containing saturated monocyclic heterocyclic group" is piperidyl group or pyrrolidinyl group, more preferably piperidyl group.

For R^{10}, preferable "nitrogen-containing saturated monocyclic heterocyclic group" is piperidyl group.

For R^{11}, preferable "nitrogen-containing saturated monocyclic heterocyclic group" is pyrrolidinyl group or piperidyl group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group, $-CO-C_{1-6}$ alkyl group and oxo group).

Being "optionally substituted by one or more substituents" means being unsubstituted or optionally substituted by at least one to the acceptable maximum number of substituents. For example, in the case of methyl group, it means being optionally substituted by 1 to 3 substituents, and in the case of ethyl group, it means being optionally substituted by 1 to 5 substituents. The substituents in the case of substitution with two or more substituents may be the same or different and the positions of the substituents are not particularly limited and may be any.

The "C_{1-6} alkyl group optionally substituted by one or more, same or different substituents" is preferably C_{1-6} alkyl group optionally substituted by the same or different 1 to 3 substituents. Particularly, "C_{1-6} alkyl group optionally substituted by one or more, same or different halogen atoms " is preferably C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, more preferably C_{1-6} alkyl group optionally substituted by three halogen atoms, and more preferably trifluoromethyl group or 2,2,2-trifluoroethyl group.

Preferable groups of each group are as follows.

[Preferable ring A]

Ring A is

(1) a nitrogen-containing saturated monocyclic heterocyclic group (i.e., -X- is $-N(R^1)-$), or

(2) a cycloalkyl group (i.e., -X- is $-C(R^7R^8)-$), and preferably

(1) an azetidinyl group or a piperidyl group, or

(2) a cyclohexyl group.

[Preferable R^2]

R^2 is preferably a cyclopropyl group or a cyclohexyl group optionally substituted by one or more, same or different substituents selected from a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by a hydroxyl group) and a C_{1-6} alkoxy group. More preferably, it is a cyclopropyl group or a cyclohexyl group optionally substituted by one or more methyl groups (said methyl group is optionally substituted by a hydroxyl group) or methoxy groups. Particularly preferably, it is cyclopropyl group, methylcyclopropyl group, methoxycyclopropyl group, tetramethylcyclopropyl group, hydroxymethylcyclopropyl group or cyclohexyl group.

[Preferable R^3 and R^4]

R^3 and R^4 are preferably not hydrogen atoms at the same time.

More preferably, one of R^3 and R^4 is a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different

substituents selected from halogen atom, hydroxyl group, methoxy group and acetyloxy group) or a C_{1-6} alkoxy group, and the other is not a hydrogen atom.

Further preferably, one of R^3 and R^4 is a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from halogen atom, hydroxyl group, methoxy group and acetyloxy group) or a C_{1-6} alkoxy group, and the other is a substituent selected from the following group, which is optionally substituted by one or more, same or different substituents selected from halogen atom, C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms or hydroxyl group), C_{1-6} alkoxy group (said C_{1-6} alkoxy group is optionally substituted by one or more, same or different halogen atoms), C_{1-6} alkoxycarbonyl group and cyano group:

·phenyl group,

·pyridyl group, and

·thiazolyl group.

Particularly preferably, one of R^3 and R^4 is a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from halogen atom, hydroxyl group, methoxy group and acetyloxy group) or a methoxy group, and the other is a substituent selected from the following group, which is optionally substituted by one or more, same or different substituents selected from halogen atom, trifluoromethyl group, trifluoromethoxy group, methoxycarbonyl group, hydroxymethyl group and cyano group:

·phenyl group,

·pyridyl group, and

·thiazolyl group.

[Preferable R^5 and R^6]

R^5 and R^6 are preferably the same or different and each is

· a hydrogen atom,

· a phenyl group optionally substituted by one or more, same or different substituents selected from hydroxyl group, halogen atom, carboxyl group and C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more hydroxyl groups or halogen atoms),

· a cycloalkyl group having 3 to 6 carbon atoms (said cycloalkyl group is optionally substituted by C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups),

· a C_{1-6} alkyl group optionally substituted by one or more, same or different substituents selected from hydroxyl group, halogen atom, phenyl group (said phenyl group is optionally substituted by halogen atom), carboxyl group and $-NR^{20}R^{21}$ (wherein R^{20} and R^{21} are as defined for the formula [1]),

· $-S(=O)_2-R^9$ wherein R^9 is phenyl group or C_{1-6} alkyl group,

· optionally substituted C_{1-6} alkoxy group,

· a pyridinyl group optionally substituted by halogen atom at the 2-position and the 6-position,

· an optionally substituted nitrogen-containing unsaturated heterocyclic group, or

· a nitrogen-containing saturated monocyclic heterocyclic group optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and $-CO-C_{1-6}$ alkyl group, or

· R^5 and R^6 may form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group selected from azetidinyl group, pyrrolidinyl group, piperidyl group, piperazinyl group, and thiomorpholinyl group, or a heterocyclic group selected from dihydroindolyl group, dihydro[1,4]oxazinyl group, and tetrahydrobenzo[b]azepinyl group, which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following group:

halogen atom,

hydroxyl group,

C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups,
carboxyl group,
acetyl group,
carbamoyl group,
amino group optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and acetyl group, and
oxo group).

More preferably, R^5 and R^6 are the same or different and each is

- a hydrogen atom,
- a phenyl group optionally substituted at the ortho-position and/or the para-position by substituents selected from hydroxyl group, halogen atom, carboxyl group and C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more hydroxyl groups or halogen atoms),
- a cyclopropyl group or a cyclopentyl group optionally substituted by C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups,
- a C_{1-6} alkyl group substituted by one or more, same or different substituent selected from hydroxyl group, halogen atom, phenyl group (said phenyl group is optionally substituted by halogen atom), carboxyl group and $-NR^{20}R^{21}$ (wherein R^{20} and R^{21} are as defined for the formula [1]),
- $-S(=O)_2-R^9$ wherein R^9 is a phenyl group or a methyl group,
- a C_{1-6} alkoxy group,
- a pyridinyl group substituted by halogen atom at the 2-position and the 6-position,
- an optionally substituted thiazolyl group, or
- a piperidin-4-yl group optionally substituted at the 1-position by one substituent selected from C_{1-6} alkyl group and $-CO-C_{1-6}$ alkyl group, or
- R^5 and R^6 may form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic

heterocyclic group selected from azetidin-1-yl group, pyrrolidin-1-yl group, piperidin-1-yl group, piperazin-1-yl group, and thiomorpholin-4-yl group, or a heterocyclic group selected from dihydroindol-1-yl group, dihydro[1,4]oxazin-1-yl group, and tetrahydrobenzo[b]azepin-1-yl group, which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following group:

halogen atom,

hydroxyl group,

C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups,

carboxyl group,

acetyl group,

carbamoyl group,

amino group optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and acetyl group, and

oxo group).

Further preferably, R^5 and R^6 are the same or different and each is

· a hydrogen atom,

· a phenyl group substituted at the ortho-position and/or the para-position by substituents selected from hydroxyl group, halogen atom, carboxyl group and C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more hydroxyl groups or halogen atoms),

· a cyclopropyl group or a cyclopentyl group substituted by C_{1-6} alkyl group substituted by one or more hydroxyl groups,

· a C_{1-6} alkyl group substituted by one substituent selected from hydroxyl group, halogen atom, phenyl group (said phenyl group is optionally substituted by halogen atom), carboxyl group and $-NR^{20}R^{21}$ (wherein R^{20} and R^{21} are as defined for the formula [1]),

· $-S(=O)_2-R^9$ wherein R^9 is a phenyl group or a methyl group,

· a C_{1-6} alkoxy group,

· a pyridin-3-yl group substituted by halogen atom at the 2-position and the 6-position,

· a thiazolyl group, or

· a piperidin-4-yl group optionally substituted at the 1-position by $-CO-C_{1-6}$ alkyl group, or

· R^5 and R^6 may form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group selected from azetidin-1-yl group, pyrrolidin-1-yl group, piperidin-1-yl group, piperazin-1-yl group, and thiomorpholin-4-yl group, or a heterocyclic group selected from dihydroindol-1-yl group, dihydro[1,4]oxazin-1-yl group, and tetrahydrobenzo[b]azepin-1-yl group, which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following group:

halogen atom,

hydroxyl group,

C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups,

carboxyl group,

acetyl group,

carbamoyl group,

amino group optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and acetyl group, and

oxo group).

Particularly preferably, R^5 and R^6 are the same or different and each is

· hydrogen atom,

· 2-fluorophenyl group,

· 2-carboxyphenyl group,

· 2-hydroxymethylphenyl group,

- 1-hydroxymethylcyclopropyl group,
- 2-hydroxyethyl group,
- 2-hydroxy-1,1-dimethylethyl group,
- 2-acetylaminoethyl group,
- 2-aminoethyl group,
- 2-dimethylaminoethyl group,
- 2-piperidin-1-yl-ethyl group,
- 2-hydroxy-1-methylethyl group,
- piperidin-4-yl group,
- 1-methyl-piperidin-4-yl group,
- 1-acetyl-piperidin-4-yl group,
- 2,2,2-trifluoroethyl group,
- 1-hydroxymethyl-2-methylpropyl group,
- 1-hydroxymethyl-2-phenylethyl group,
- 2-hydroxy-1-phenylethyl group,
- 1-hydroxymethyl-3-methylbutyl group,
- 2-hydroxyphenyl group,
- 1-hydroxymethyl-cyclopentyl group,
- benzenesulfonyl group,
- 4-trifluoromethylphenyl group,
- 2,4-difluorophenyl group,
- 1-carboxy-2-methylpropyl group,
- thiazol-2-yl group,
- isopropoxy group,
- 4-fluorobenzyl group,
- 2,6-dichloropyridin-3-yl group,
- ethoxy group, or
- mesyl group, or
- R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group or a heterocyclic group which is a fused ring of said heterocycle and a carbon ring, which is selected from the following group:

azetidin-1-yl group,

3-hydroxyazetidin-1-yl group,

3-hydroxymethylazetidin-1-yl group,
3-acetylazetidin-1-yl group,
3-acetylaminoazetidin-1-yl group,
3-hydroxypyrrolidin-1-yl group,
3,3-difluoropyrrolidin-1-yl group,
3,3,4,4-tetrafluoropyrrolidin-1-yl group,
2-hydroxymethylpyrrolidin-1-yl group,
2-aminopyrrolidin-1-yl group,
2-acetylaminopyrrolidin-1-yl group,
2-dimethylaminopyrrolidin-1-yl group,
3-oxo-pyrrolidin-1-yl group,
4-hydroxypiperidin-1-yl group,
4,4-difluoropiperidin-1-yl group,
4-hydroxymethylpiperidin-1-yl group,
4-carboxypiperidin-1-yl group,
3-hydroxypiperidin-1-yl group,
4-carbamoylpiperidin-1-yl group,
4-aminopiperidin-1-yl group,
4-dimethylaminopiperidin-1-yl group,
4-acetylaminopiperidin-1-yl group,
4-methylpiperazin-1-yl group,
4-isopropylpiperazin-1-yl group,
4-acetylpiperazin-1-yl group,
1,1-dioxothiomorpholin-4-yl group,
3-oxo-piperidin-1-yl group,
4-oxo-piperidin-1-yl group,
2,3-dihydroindol-1-yl group,
2,3-dihydro[1,4]oxazin-1-yl group, and
2,3,4,5-tetrahydrobenzo[b]azepin-1-yl group.

Further preferably, R^5 and R^6 are not hydrogen atoms at the same time. More preferably, one of R^5 and R^6 is a hydrogen atom and the other is not a hydrogen atom.

[Preferable R^{10}]

R^{10} is preferably

- a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally

substituted by one or more, same or different substituents selected from hydroxyl group, phenyl group and $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form a piperidyl group together with the nitrogen atom bonded thereto), or

· a piperidyl group (said piperidyl group is optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and $-CO-C_{1-6}$ alkyl group).

R^{10} is more preferably

· a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from hydroxyl group, phenyl group and $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is C_{1-6} alkyl group, or R^{26} and R^{27} optionally form a piperidyl group together with the nitrogen atom bonded thereto), or

· a piperidin-4-yl group (said piperidin-4-yl group is optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and $-CO-C_{1-6}$ alkyl group).

R^{10} is further preferably

· a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from hydroxyl group, phenyl group and $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is C_{1-6} alkyl group, or R^{26} and R^{27} optionally form a piperidyl group together with the nitrogen atom bonded thereto), or

· a piperidin-4-yl group (said piperidin-4-yl group is optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and $-CO-C_{1-6}$ alkyl group).

R^{10} is particularly preferably

· methyl group,

· 2-hydroxyethyl group,

· 2-dimethylaminoethyl group,

· 2-piperidin-1-yl-ethyl group,

· piperidin-4-yl group,

· 1-methyl-piperidin-4-yl group,

· benzyl group, or

· 1-acetyl-piperidin-4-yl group.

[Preferable R^{11}]

R^{11} is preferably

· a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to g):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, -CO-cycloalkyl group, or $-S(=O)_2-C_{1-6}$ alkyl group,

d) a carbamoyl group,

e) a carboxyl group,

f) a phenoxy group, and

g) a fluorophenyl group),

· a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group optionally substituted by one or more, same or different halogen atoms, and

b) a C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups),

· an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) one or more, same or different halogen atoms,

b) a C_{1-6} alkyl group optionally substituted by one or more, same or different halogen atoms, and

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

· a carboxyl group, or

· a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or

more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group).

R^{11} is more preferably

· a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to g):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, -CO-cycloalkyl group, or $-S(=O)_2-C_{1-6}$ alkyl group,

d) a carbamoyl group,

e) a carboxyl group,

f) a phenoxy group, and

g) a fluorophenyl group),

· a cyclopropyl group (said cyclopropyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group optionally substituted by one or more, same or different halogen atoms, and

b) a C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups),

· a phenyl group (said phenyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) one or more, same or different halogen atoms,

b) a C_{1-6} alkyl group optionally substituted by one or more, same or different halogen atoms, and

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

· a carboxyl group, or

· a nitrogen-containing saturated monocyclic heterocyclic group selected from a pyrrolidinyl group and a piperidyl group (said

heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group).

R^{11} is further preferably

· a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to g):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, -CO-cycloalkyl group, or $-S(=O)_2-C_{1-6}$ alkyl group,

d) a carbamoyl group,

e) a carboxyl group,

f) a phenoxy group, and

g) a fluorophenyl group),

· a cyclopropyl group (said cyclopropyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group optionally substituted by one or more, same or different halogen atoms, and

b) a C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups),

· a phenyl group (said phenyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) one or more, same or different halogen atoms,

b) a C_{1-6} alkyl group optionally substituted by one or more, same or different halogen atoms, and

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

· a carboxyl group, or

· a nitrogen-containing saturated monocyclic heterocyclic group

selected from a pyrrolidin-2-yl group and a piperidin-4-yl group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group).

R^{11} is particularly preferably

- 2,2,2-trifluoroethyl group,
- hydroxymethyl group,
- 3-hydroxy-propyl group,
- 2-hydroxy-1,1-dimethyl-ethyl group,
- aminomethyl group,
- 2-amino-ethyl group,
- 1-amino-1-methyl-ethyl group,
- 1-amino-2-methyl-propyl group,
- methylamino-methyl group,
- dimethylamino-methyl group,
- acetylamino-methyl group,
- 1-acetylamino-ethyl group,
- 2-acetylamino-ethyl group,
- 1-acetylamino-1-methyl-ethyl group,
- 1-acetylamino-2-methyl-propyl group,
- isobutyrylamino-methyl group,
- cyclopropanecarbonyl-amino-methyl group,
- methanesulfonylamino-methyl group,
- 2-carbamoyl-ethyl group,
- cyclopropyl group,
- 1-(4-fluoro-phenyl)-cyclopropyl group,
- 1-methyl-cyclopropyl group,
- 1-hydroxymethyl-cyclopropyl group,
- pyrrolidin-1-yl group,
- pyrrolidin-2-yl group,
- piperidin-4-yl group,
- 1-methyl-pyrrolidin-2-yl group,

- 1-methyl-piperidin-4-yl group,
- 1-acetyl-pyrrolidin-2-yl group,
- 1-acetyl-piperidin-4-yl group,
- 2-carboxy-2-methylpropyl group,
- phenoxymethyl group,
- 2-chlorophenyl group,
- 3-chlorophenyl group,
- 4-chlorophenyl group,
- carboxyl group,
- 4-fluorobenzyl group,
- 3-trifluoromethylphenyl group,
- 3-methoxyphenyl group, or
- 5-oxo-pyrrolidin-2-yl group.

The salt of the compound of the present invention is preferably a pharmaceutically acceptable salt. The salt of the compound of the present invention represented by the formula [1'] can be produced by a conventional method. The salt of the compound of the present invention represented by the formula [1'] can be mentioned by reacting compound [1'] (hereinafter compound [1'] and salts thereof are also to be collectively referred to as the compound of the present invention) with, for example, inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like; organic acids such as oxalic acid, malonic acid, citric acid, fumaric acid, lactic acid, malic acid, succinic acid, tartaric acid, acetic acid, trifluoroacetic acid, gluconic acid, ascorbic acid, methanesulfonic acid, benzenesulfonic acid and the like; inorganic bases such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonium hydroxide and the like; organic bases such as methylamine, diethylamine, triethylamine, triethanolamine, ethylenediamine, tris(hydroxymethyl)methylamine, guanidine, choline, cinchonine and the like; amino acids such as lysine, arginine, alanine and the like, and the like. The present invention also encompasses water-containing products, hydrates and solvates of the

compound of the present invention.

In addition, the compound of the present invention has various isomers. For example, E form and Z form can be present as geometric isomers, when an asymmetric carbon atom is present, enantiomer and diastereomer are present as stereoisomers based thereon, and tautomers can also be present. Therefore, the present invention encompasses all of these isomers and mixtures thereof. Moreover, the present invention encompasses, besides the compound of the present invention, prodrug compounds and metabolite compounds of these compounds as equivalent compounds.

As used herein, the "prodrug" is a derivative having a chemically or metabolically decomposable group, which shows a pharmaceutical activity upon decomposition by hydrolysis or solvolysis, or under physiological conditions. A prodrug is used for, for example, improving absorption by oral administration or targeting the object site. Inasmuch as what the chemically or metabolically decomposable group is, and how to introduced the group into a compound have been sufficiently established in the field of pharmaceutical agents, such known techniques can be employed in the present invention. As the moiety to be modified for producing a prodrug, for example, highly reactive functional groups such as a hydroxyl group, a carboxyl group, an amino group, a thiol group and the like in the compound of the present invention can be mentioned.

For example, a derivative wherein a substituent such as -CO-C_{1-6} alkyl group, -CO_2-C_{1-6} alkyl group, -CONH-C_{1-6} alkyl group, -CO-C_{2-6} alkenyl group, -CO_2-C_{2-6} alkenyl group, -CONH-C_{2-6} alkenyl group, -CO-aryl group, -CO_2-aryl group, -CONH-aryl group, -CO-heterocyclic group, -CO_2-heterocyclic group, -CONH-heterocyclic group (the C_{1-6} alkyl group, C_{2-6} alkenyl group, aryl group and heterocyclic group are each optionally substituted by halogen atom, C_{1-6} alkyl group, hydroxyl group, C_{1-6} alkoxy group, carboxyl group, amino group, amino acid residue, -PO_3H_2, -SO_3H, -CO-polyethylene glycol residue, -CO_2-

polyethylene glycol residue, -CO-polyethylene glycol monoalkyl ether residue, $-CO_2$-polyethylene glycol monoalkyl ether residue and the like) and the like has been introduced into a hydroxyl group can be mentioned.

In addition, a derivative wherein a substituent such as -CO-C_{1-6} alkyl group, $-CO_2-C_{1-6}$ alkyl group, -CO-C_{2-6} alkenyl group, $-CO_2-C_{2-6}$ alkenyl group, -CO-aryl group, $-CO_2$-aryl group, -CO-heterocyclic group, $-CO_2$-heterocyclic group (the C_{1-6} alkyl group, C_{2-6} alkenyl group, aryl group and heterocyclic group are each optionally substituted by halogen atom, C_{1-6} alkyl group, hydroxyl group, C_{1-6} alkoxy group, carboxyl group, amino group, amino acid residue, $-PO_3H_2$, $-SO_3H$, -CO-polyethylene glycol residue, $-CO_2$-polyethylene glycol residue, -CO-polyethylene glycol monoalkyl ether residue, $-CO_2$-polyethylene glycol monoalkyl ether residue, $-PO_3H_2$ and the like) and the like has been introduced into an amino group can be mentioned.

Furthermore, a derivative wherein a substituent such as C_{1-6} alkoxy group, aryloxy group (the C_{1-6} alkoxy group and aryloxy group are each optionally substituted by halogen atom, C_{1-6} alkyl group, hydroxyl group, C_{1-6} alkoxy group, carboxyl group, amino group, amino acid residue, $-PO_3H_2$, $-SO_3H$, polyethylene glycol residue, polyethylene glycol monoalkyl ether residue and the like) and the like has been introduced into a carboxyl group can be mentioned.

In the above, the "heterocyclic group" is a 5-membered or 6-membered saturated or unsaturated (including partial unsaturation and complete unsaturation) monocyclic heterocyclic group having, besides carbon atom, at least one, preferably 1 to 4, hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, or a fused ring group of the heterocycles or a fused ring group of the heterocycle and a carbon ring selected from benzene, cyclopentane and cyclohexane.

As the "5-membered or 6-membered saturated monocyclic heterocyclic group", for example, pyrrolidinyl group, tetrahydrofuryl group, tetrahydrothienyl group, imidazolidinyl

group, pyrazolidinyl group, 1,3-dioxolanyl group, 1,3-oxathioranyl group, oxazolidinyl group, thiazolidinyl group, piperidinyl group, piperazinyl group, tetrahydropyranyl group, tetrahydrothiopyranyl group, dioxanyl group, morpholinyl group, thiomorpholinyl group, 2-oxopyrrolidinyl group, 2-oxopiperidinyl group, 4-oxopiperidinyl group, 2,6-dioxopiperidinyl group and the like can be mentioned.

As the "5-membered or 6-membered unsaturated monocyclic heterocyclic group", for example, pyrrolyl group, furyl group, thienyl group, imidazolyl group, 1,2-dihydro-2-oxoimidazolyl group, pyrazolyl group, diazolyl group, oxazolyl group, isoxazolyl group, thiazolyl group, isothiazolyl group, triazolyl group(1,2,4-triazolyl group, 1,2,3-triazolyl group), tetrazolyl group, 1,3,4-oxadiazolyl group, 1,2,4-oxadiazolyl group, 1,3,4-thiadiazolyl group, 1,2,4-thiadiazolyl group, furazanyl group, pyridyl group, pyrimidinyl group, 3,4-dihydro-4-oxopyrimidinyl group, pyridazinyl group, pyrazinyl group, 1,3,5-triazinyl group, imidazolinyl group, pyrazolinyl group, oxazolinyl group(2-oxazolinyl group, 3-oxazolinyl group, 4-oxazolinyl group), isooxazolinyl group, thiazolinyl group, isothiazolinyl group, pyranyl group, 2-oxopyranyl group, 2-oxo-2,5-dihydrofuranyl group and 1,1-dioxo-1H-isothiazolyl group can be mentioned.

As the "heterocyclic group which is a fused ring", for example, indolyl group (e.g., 4-indolyl group, 7-indolyl group etc), isoindolyl group, 1,3-dihydro-1,3-dioxoisoindolyl group, benzofuranyl group (e.g., 4-benzofuranyl group, 7-benzofuranyl group etc), indazolyl group, isobenzofuranyl group, benzothiophenyl group (e.g., 4-benzothiophenyl group, 7-benzothiophenyl group etc), benzooxazolyl group (e.g., 4-benzooxazolyl group, 7-benzooxazolyl group etc), benzimidazolyl group (e.g., 4-benzimidazolyl group, 7-benzimidazolyl group etc), benzothiazolyl group (e.g., 4-benzothiazolyl group, 7-benzothiazolyl group etc), indolizinyl group, quinolyl group, isoquinolyl group, 1,2-dihydro-2-oxoquinolyl group,

quinazolinyl group, quinoxalinyl group, cinnolinyl group, phthalazinyl group, quinolizinyl group, puryl group, pteridinyl group, indolinyl group, isoindolinyl group, 5,6,7,8-tetrahydroquinolyl group, 1,2,3,4-tetrahydroquinolyl group, 2-oxo-1,2,3,4-tetrahydroquinolyl group, benzo[1,3]dioxolyl group, 3,4-methylenedioxypyridyl group, 4,5-ethylenedioxypyrimidinyl group, chromenyl group, chromanyl group, isochromanyl group and the like can be mentioned.

The "pharmaceutical composition" includes, besides what is called a "composition" comprising an active ingredient as a pharmaceutical agent and a combination drug and the like, a combination agent with other drug, and the like. It is needless to say that the pharmaceutical composition of the present invention can be concurrently used with any other drug within the range acceptable in clinical situations. Therefore, the present pharmaceutical composition can also be considered a pharmaceutical composition to be combined with other drug.

Moreover, the pharmaceutical composition of the present invention can be administered to not only human but also other mammals (mouse, rat, hamster, rabbit, cat, dog, bovine, horse, sheep, monkey etc.). Therefore, the pharmaceutical composition of the present invention is also useful as a pharmaceutical product for animals, not to mention human.

The compound of the present invention or a salt thereof can be mixed with a pharmaceutically acceptable carrier, and administered orally or parenterally as tablet, pill, powder, granule, suppository, injection, eye drop, liquid, capsule, troche, aerosol, elixir, suspension, emulsion, syrup and the like.

As the "pharmaceutically acceptable carrier", various organic or inorganic carrier substances conventionally used as preparation materials are employed, which are added as excipient, lubricant, binder, disintegrant, solvent, dissolution aids, suspending agent, isotonicity agent, buffer, soothing agent and the like. Where necessary,

preparation additives such as preservative, antioxidant, coloring agent, sweetening agent and the like can also be used. As examples of the above-mentioned excipient, lactose, sucrose, D-mannitol, starch, crystalline cellulose, light silicic anhydride and the like can be mentioned. As the above-mentioned lubricant, for example, magnesium stearate, calcium stearate, talc, colloidal silica and the like can be mentioned. As examples of the above-mentioned binder, polymer compound such as crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone and the like can be mentioned. As examples of the above-mentioned disintegrant, starch, carboxymethylcellulose, carboxymethylcellulose calcium, croscarmellose sodium, sodium carboxymethyl starch and the like can be mentioned. As examples of the above-mentioned solvent, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil, propylene glycol esters of fatty acids and the like can be mentioned. As examples of the above-mentioned dissolution aids, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the like can be mentioned. As examples of the above-mentioned suspending agent, surfactants such as stearyl triethanolamine, sodium lauryl sulfate, lauryl aminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glyceryl monostearate and the like; polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose and the like can be mentioned. As examples of the above-mentioned isotonicity agent, sodium chloride, glycerol, D-mannitol and the like can be mentioned. As examples of the above-mentioned buffer, buffers such as phosphate, acetate, carbonate, citrate and the like, and the like can be mentioned. As examples of the

above-mentioned soothing agent, benzyl alcohol and the like can be mentioned. As examples of the above-mentioned preservative, paraoxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like can be mentioned. As examples of the above-mentioned antioxidant, sulfite, ascorbic acid and the like can be mentioned. As examples of the above-mentioned sweetening agent, aspartam, saccharin sodium, stevia and the like can be mentioned. As examples of the above-mentioned coloring agent, foodcolors such as Food Color Yellow No. 5, Food Color Red No. 2 and Food Color Blue No. 2 and the like, food lake colors, iron oxide and the like can be mentioned.

The "11βHSD1 inhibitor" means disappearance or attenuation of the activity of 11βHSD1 by specifically inhibiting the function thereof as an enzyme, and means, for example, specific inhibition of the function of 11βHSD1 under the conditions of the below-mentioned Experimental Example 1, and preferably means the concentration necessary to achieve 50% inhibition of 11βHSD1 under the conditions of the below-mentioned Experimental Example 1 of less than 10 μM, preferably less than 1 μM, more preferably less than 100 nM, and still more preferably less than 10 nM.

The "pathology involving glucocorticoid" means, for example,

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis

and the like.

When the compound of the present invention is used as the drug for the treatment or prophylaxis of pathology showing involvement of glucocorticoid, it can be systemically or topical, and orally or parenterally administered. While the dose varies depending on the age, body weight, condition, treatment effect and the like, for example, it can be generally administered within the range of 0.1 mg to 1 g per administration to an adult once to several times a day. The compound of the present invention can also be used as a drug for the treatment or prophylaxis of the aforementioned diseases in, not to mention human, animals other than human, particularly mammals. The same applies to the use of the compound of the present invention as a drug for the treatment or prophylaxis of

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis

and the like.

To produce a preparation of the compound of the present invention such as a solid composition or liquid composition for oral administration, or an injection for parenteral administration and the like, the compound can be admixed

additives such as a suitable diluent, a dispersing agent, an adsorbent, a solubilizer and the like. In addition, the pharmaceutical composition of the present invention may have known form such as tablet, pill, powder, granule, suppository, injection, eye drop, liquid, capsule, troche, aerosol, elixir, suspension, emulsion, syrup and the like.

When the pharmaceutical composition of the present invention is, for example, a solid preparation such as tablet, pill, powder, granule etc., the additive includes, for example, lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium aluminometasilicate, silicic anhydride powder and the like. When a tablet or pill is to be prepared, a film coating of gastrosoluble or enteric substance such as sucrose, gelatin, hydroxypropylcellulose, or hydroxymethylcellulose phthalate etc. may be applied as necessary, or a multi-layer tablet having two or more layers may be produced.

The compound, pharmaceutical composition, or drug of the present invention can be used in combination with (hereinafter to be also referred to combined use) other pharmaceutical composition or drug (hereinafter to be also referred to as a combination drug).

The timing of administration of the pharmaceutical composition or drug of the present invention, and a combination drug is not limited, and they may be administered to the administration subject in the form of a combined drug, simultaneously administered, or administered in a staggered manner. Moreover, a pharmaceutical agent which is characteristically a kit containing the pharmaceutical composition or drug of the present invention and a combination drug may be administered. The dose of the combination drug may be one clinically employed, which can be appropriately determined depending on the subject of administration, age and body weight of the administration subject, condition, administration time, dosage form, administration method,

combination and the like. The mode of administration of the combination drug is not particularly limited, and may be any as long as the pharmaceutical composition or drug of the present invention, and a combination drug are combined.

A pharmaceutical agent comprising 1 to 3 agents selected from the following (1) to (5) and the compound of the present invention or a salt thereof in combination:

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension

means pharmaceutical agents such as a case in which the "pharmaceutical agent" is a combined drug, a case in which the "pharmaceutical agent" is a kit containing a drug containing said "1 to 3 agents selected from (1) to (5)" and a drug containing the compound of the present invention, a case in which the "pharmaceutical agent" and the drug containing the compound of the present invention are administered simultaneously or at certain intervals, and the like. This pharmaceutical agent is preferably an agent for the treatment or prophylaxis of a pathology involving glucocorticoid.

As the combination drug,

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications, and

(5) an agent for the treatment or prophylaxis of hypertension,

can be mentioned, and 1 to 3 agents therefrom and the compound of the present invention can be used in combination.

As the "agent for the treatment or prophylaxis of

hyperlipidemia", for example,

(1) fibrate drugs (PPAR α receptor agonists),

(2) PPAR-δ receptor agonists,

(3) microsomal triglyceride transfer protein (MTP) inhibitors,

(4) cholesteryl ester transfer protein (CETP) inhibitors,

(5) statin drugs (HMG-CoA reductase inhibitors),

(6) anion exchange resins,

(7) probucol,

(8) nicotinic acid drugs,

(9) phytosterol,

(10) apolipoprotein-A1 (Apo-A1) inducers,

(11) lipoprotein lipase (LPL) activators,

(12) endothelial lipase inhibitors,

(13) ezetimibe,

(14) IBAT inhibitors,

(15) squalene synthase inhibitors,

(16) ACAT inhibitors,

(17) LXR receptor agonists,

(18) FXR receptor agonists,

(19) FXR receptor antagonists, and

(20) adenosine A1 agonists

can be mentioned, and specifically, clofibrate, bezafibrate, fenofibrate, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, pitavastatin, rosuvastatin, cerivastatin, cholestyramine, colestimide, tocopherol nicotinate, nicomol, niceritrol, soysterol, gamma oryzanol and the like can be mentioned.

As the "agent for the treatment or prophylaxis of obesity", for example,

(1) leptin drugs,

(2) pancreatic lipase inhibitors,

(3) noradrenaline serotonin reuptake inhibitors,

(4) cannabinoid receptor antagonists,

(5) monoamine reuptake inhibitors,

(6) diacylglycerol acyltransferase (DGAT) inhibitors,

(7) glucose-dependent insulinotropic polypeptide (GIP) receptor antagonists,

(8) leptin receptor agonists,

(9) bombesin receptor subtype 3 (BRS-3) agonists,

(10) perilipin inhibitors,

(11) acetyl-CoA carboxylase 1 (ACC1) inhibitors,

(12) acetyl-CoA carboxylase 2 (ACC2) inhibitors,

(13) fatty acid synthase inhibitors,

(14) sn-1-acyl-glycerol-3-phosphate acyltransferase (AGPAT) inhibitors,

(15) pancreatic phospholipase A2 (pPLA2) inhibitors,

(16) melanocortin (MC) receptor agonists,

(17) neuropeptide Y5 (NPY5) receptor antagonists,

(18) uncoupling protein (UCP) inducer or activators,

(19) carnitine O-palmitoyltransferase 1 (CPT-1) activators,

(20) CCK1 (CCKA) agonists,

(21) Ciliary Neurotrophic Factor (CNTF),

(22) CRF 2 agonists,

(23) neuropeptide Y2 (NPY2) receptor antagonists,

(24) neuropeptide Y4 (NPY4) receptor antagonists,

(25) thyroid hormone receptor beta agonists,

(26) growth hormones,

(27) ATP citrate lyase inhibitors,

(28) 5-HT6 antagonists, and

(29) 5-HT2C agonists

can be mentioned, and specifically, leptin, orlistat, sibutramine, rimonabant, and mazindol and the like can be mentioned.

As the "agent for the treatment or prophylaxis of diabetes", for example,

(1) insulin preparations (injection),

(2) low molecular insulin oral preparations,

(3) sulfonylurea receptor agonists (SU agents),

(4) non-sulfonylurea insulin secretagogues (SU agents),

(5) potassium dependent ATP (KATP) channel openers,

(6) α glucosidase inhibitors,

(7) α amylase inhibitors,

(8) insulin sensitizer,

(9) low molecular tGLP-1 receptor agonists,

(10) tGLP-1 peptide analogs,

(11) dipeptidyl peptidase IV (DPP-IV) inhibitors,

(12) glucagon receptor antagonists,

(13) glucocorticoid receptor antagonists,

(14) biguanides,

(15) SGLUT inhibitors,

(16) fructose-1,6-bisphosphatase (FBPase) inhibitors,

(17) glycogen synthase kinase 3 (GSK-3) inhibitors,

(18) phosphoenolpyruvate carboxykinase (PEPCK) inhibitors,

(19) protein tyrosine phosphatase 1B (PTPase 1B) inhibitors,

(20) SH2 domain-containing inositol phosphatase (SHIP2) inhibitors,

(21) glycogen phosphorylase (GP) inhibitors,

(22) glucokinase activators,

(23) GPR40 receptor agonists,

(24) pyruvate dehydrogenase kinase (PDHK) inhibitors,

(25) glutamine: fructose-6-phosphate aminotransferase (GFAT) inhibitors,

(26) antioxidants; nitric oxide scavengers,

(27) carnitine O-palmitoyltransferase 1 (CPT-1) inhibitors,

(28) growth hormone-releasing factors (GHRF),

(29) triacylglycerol lipase (hormone sensitive lipase) inhibitors,

(30) PPAR γ receptor agonists,

(31) PPAR γ receptor antagonists,

(32) PPAR α/γ receptor agonists,

(33) AMP-activated protein kinase (AMPK) activators,

(34) adiponectin receptor agonists, and

(35) β3 adrenaline receptor agonists

can be mentioned, and specifically, insulin, tolbutamide, glyclopyramide, acetohexamide, chlorpropamide, glybuzole,

glibenclamide, gliclazide, glimepiride, mitiglinide, repaglinide, nateglinide, voglibose, acarbose, miglitol, rosiglitazone maleate, metformin hydrochloride, pioglitazone hydrochloride, buformin hydrochloride and the like can be mentioned.

As the "agent for the treatment or prophylaxis of diabetic complications", for example,

(1) protein kinase C β (PKCβ) inhibitor,

(2) angiotensin II receptor antagonist,

(3) aldose reductase inhibitor,

(4) angiotensin converting enzyme (ACE) inhibitor,

(5) advanced glycation end products (AGE) production inhibitors,

(6) therapeutic agents for neuropathy, and

(7) therapeutic agents for diabetic nephropathy

can be mentioned, and specifically, epalrestat (kinedak), mexiletine hydrochloride, imidapril hydrochloride and the like can be mentioned.

As the "agent for the treatment or prophylaxis of hypertension", for example,

(1) thiazide diuretics,

(2) thiazide-like diuretics,

(3) loop diuretics,

(4) K maintenance diuretics,

(5) β blockers,

(6) α,β blockers,

(7) α blockers,

(8) central sympathetic neurosuppressants,

(9) peripheral sympathetic neurosuppressants (rauwolfia preparations),

(10) Ca antagonist (benzothiazepin),

(11) Ca antagonists (dihydropyridine),

(12) vasodilators,

(13) angiotensin converting enzyme (ACE) inhibitors,

(14) angiotensin II receptor antagonists,

(15) nitrate drug,

(16) endothelin ETA receptor antagonists,

(17) endothelin-converting enzyme inhibitors; Neprilysin inhibitors,

(18) prostaglandin; prostanoid FP agonists,

(19) renin inhibitors,

(20) NOS3 expression enhancers; prostacyclin analogs,

(21) phosphodiesterase V (PDE5A) inhibitors,

(22) prostacyclin analogs, and

(23) aldosterone antagonists

can be mentioned, and specifically, hydrochlorothiazide, trichlormethiazide, benzylhydrochlorothiazide, meticrane, indapamide, tripamide, chlorthalidone, mefruside, furosemide, spironolactone, triamterene, atenolol, bisoprolol fumarate, betaxolol hydrochloride, bevantolol hydrochloride, metoprolol tartrate, acebutolol hydrochloride, celiprolol hydrochloride, nipradilol, tilisolol hydrochloride, Nadolol, propranolol hydrochloride, indenolol hydrochloride, carteolol hydrochloride, pindolol, pindolol sustained-release preparation, bunitrolol hydrochloride, penbutolol sulfate, bopindolol malonate, amosulalol hydrochloride, arotinolol hydrochloride, carvedilol, labetalol hydrochloride, urapidil, terazosin hydrochloride, doxazosin mesylate, bunazosin hydrochloride, prazosin hydrochloride, phentolamine mesylate, clonidine hydrochloride, guanfacine hydrochloride, guanabenz acetate, methyldopa, reserpine, rescinnamine, amlodipine besilate, aranidipine, efonidipine hydrochloride, cilnidipine, nicardipine hydrochloride, nisoldipine, nitrendipine, nifedipine, nifedipine sustained-release preparation, nilvadipine, barnidipine hydrochloride, felodipine, benidipine hydrochloride, manidipine hydrochloride, azelnidipine, diltiazem hydrochloride, hydrazine hydrochloride, todoralazine hydrochloride, budralazine, cadralazine, captopril, enalapril maleate, alacepril, delapril hydrochloride, cilazapril, lisinopril, benazepril hydrochloride, imidapril hydrochloride,

temocapril hydrochloride, quinapril hydrochloride, trandolapril, perindopril erbumine, candesartancilexetil, valsartan, termisartan, olmesartan medoxomil, sodium nitroprusside, nitroglycerin and the like can be mentioned.

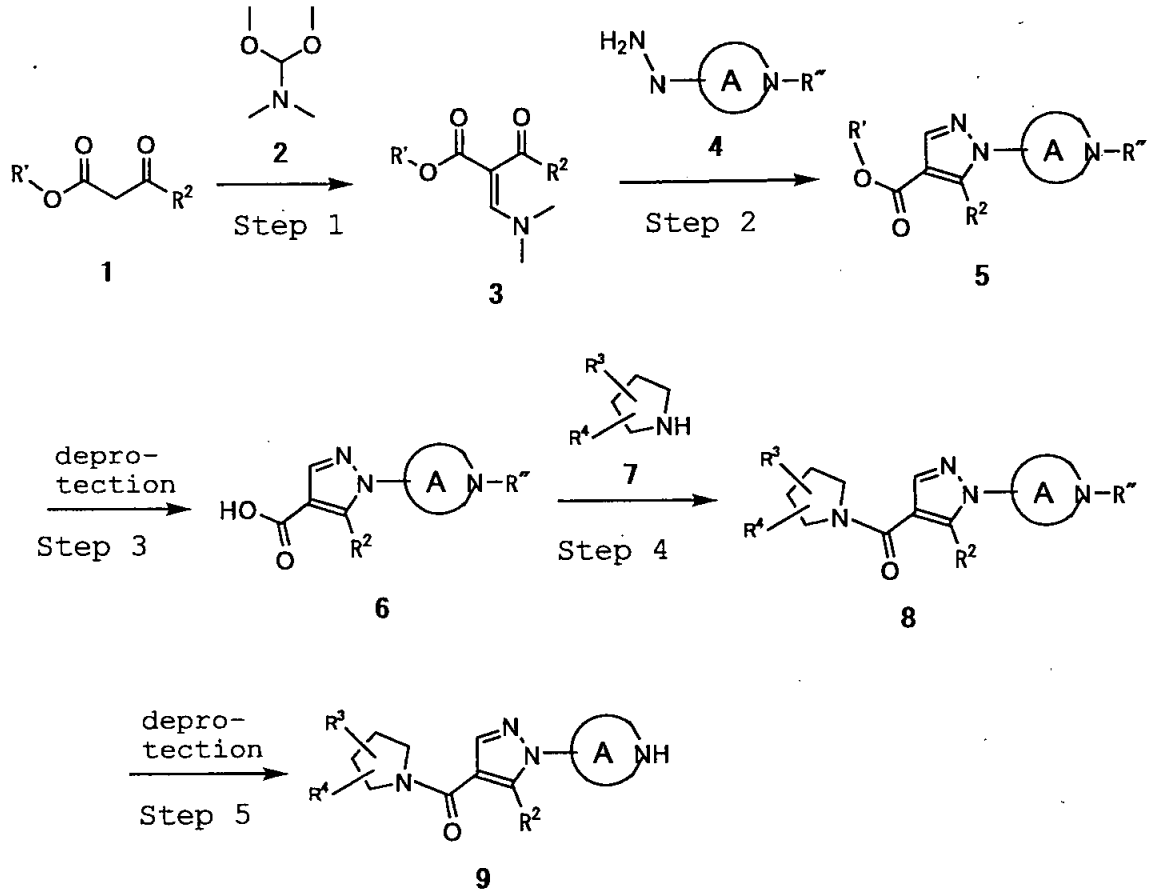
As the combination drug, a drug that raises the blood glucocorticoid level, such as adrenal corticosteroid and the like can be mentioned. The blood glucocorticoid means not only endogenous glucocorticoids, such as corticosterone, cortisol and the like, but also exogenous glucocorticoids due to the administration of adrenal corticosteroid. One to three agents therefrom and the compound of the present invention can be used in combination.

Some examples of the production methods of the compounds of the present invention are shown in the following. However, the production methods of the compounds of the present invention are not limited to these examples. Even in the absence of description in the production method, efficient production can be afforded, where necessary, by introducing a protecting group into a functional group followed by deprotection in a subsequent step, by exchanging the order of respective steps. As the protecting group, for example, a carboxy-protecting group (here, the carboxy-protecting group means those generally used in the field of synthetic organic chemistry, such as methyl group, ethyl group, propyl group, tert-butyl group, benzyl group, p-methoxybenzyl group and the like, which are in the form of esters capable of being easily led to carboxylic acid by hydrolysis, catalytic hydrogenation and the like), an amino-protecting group (here, the amino-protecting group means those generally used in the field of organic synthesis chemistry, such as tert-butoxycarbonyl group, benzyloxycarbonyl group, benzyl group and the like, which can be easily led to an amino group by hydrolysis, catalytic hydrogenation and the like), a hydroxyl group-protecting group (here, the hydroxyl group-protecting group means those generally used in the field of organic synthesis chemistry,

such as tetrahydropyranyl group, methoxymethyl group, methoxyethoxymethyl group, benzyloxymethyl group, benzyl group, p-methoxybenzyl group, p-nitrobenzyl group, trimethylsilyl group, t-butyldimethylsilyl group, acetyl group, benzoyl group, allyl group, t-butyl group and the like, which can be easily led to a hydroxyl group by hydrolysis, catalytic hydrogenation and the like), and the like can be mentioned. The workup after reaction in each step can be applied by a typical method, wherein isolation and purification is performed by selecting or combining conventional methods as necessary, such as crystallization, recrystallization, silica gel chromatography, preparative HPLC and the like.

Production Method 1

In the compound [1'] of the present invention, a compound wherein -X- is -NH- can be produced by the following steps.



1 3 5 6 8 9

wherein R' is a carboxy-protecting group (here, the carboxy-protecting group means those generally used in the field of organic synthesis chemistry, such as methyl group, ethyl group,

propyl group, tert-butyl group, benzyl group, p-methoxybenzyl group and the like), which is in the form of esters capable of being easily led to carboxylic acid by hydrolysis, catalytic hydrogenation and the like, R″ is an amino protecting group (here, the amino-protecting group means those generally used in the field of organic synthesis chemistry, such as tert-butoxycarbonyl group, benzyloxycarbonyl group, benzyl group and the like) which can be easily removed by hydrolysis, catalytic hydrogenation and the like, and other symbols are as defined above.

Step 1

Compound (3) can be obtained by reacting β-ketoester (1) synthesized by a known method with dimethylformamide dimethylacetal (2) in a solvent or in the absence of a solvent. As the solvent, methanol, ethanol, benzene, toluene, xylene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 250°C. The reaction time is generally 1 hr to 24 hr. The amount of dimethylformamide dimethylacetal (2) to be used is generally about 1.5 - about 3 mol, per 1 mol of β-ketoester (1). The amount of the solvent to be used is not particularly limited and can be appropriately determined depending on the kind and the amount of use of the reaction substrate (β-ketoester (1) and dimethylformamide dimethylacetal (2)), reaction temperature, reaction time and the like (the same applies to the amount of the solvent to be used in each Step to be explained below).

Step 2: Step for constructing pyrazole ring

Compound (5) is obtained by reacting hydrazine (4) synthesized by a known method with compound (3) in a solvent. As the solvent, methanol, ethanol, n-propanol, n-butanol, isopropanol, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the

like can be mentioned. The reaction temperature is generally 20°C to 250°C. The reaction time is generally 1 hr to 24 hr. The amount of hydrazine (4) to be used is generally about 1 - about 2 mol, per 1 mol of compound (3). When hydrazine (4) is a salt, the reaction is carried out in the presence of a base (the amount of the base to be used is generally about 1 - about 2 mol, per 1 mol of compound (3)), such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like.

Step 3: Deprotection step of carboxyl-protecting group

Compound (6) is obtained by eliminating the carboxyl-protecting group R' of compound (5) by a known method.

Step 4: Amidation step

Compound (8) is obtained by reacting compound (6) with amine (7) in a solvent in the presence of a condensing agent and an additive. As the condensing agent, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), diisopropylcarbodiimide, 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA) and the like can be mentioned. As the additive, 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinic imide (HOSu), 4-dimethylaminopyridine (DMAP) and the like can be mentioned. As the solvent, dichloromethane, chloroform, acetonitrile, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of amine (7) to be used is generally about 1 - about 1.5 mol per 1 mol of compound (6). In addition, the amount of the condensing agent and the additive to be used is generally about 1 - about 1.5 mol and about 1 - about 1.5 mol, respectively, per 1 mol of compound (6). When amine (7) is a

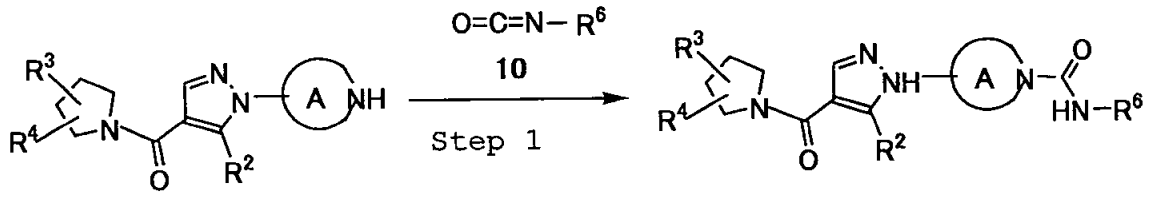
salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like. Alternatively, carboxylic acid (6) may be led to an acid halide or a mixed acid anhydride and reacted with amine (7) in the presence of a base. The amount of the base to be used is generally about 1 - about 1.5 mol per 1 mol of compound (6).

Step 5: Deprotection step of amino protecting group

Compound (9) is obtained by eliminating the amino protecting group R″ of compound (8) by a known method. Where necessary, it may be converted to a salt by a known method.

Production Method 2

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is $-CONR^5R^6$ wherein R^5 is a hydrogen atom can be produced by the following Steps.



9 11

wherein each symbol is as defined above.

Step 1: Ureation step

1) When R^6 is other than hydrogen

Compound (11) is obtained by reacting compound (9) with isocyanate (10) in a solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of isocyanate (10) to be used is generally about 1 - about 2 mol per 1 mol of compound

(9). When amine (9) is a salt, the reaction is carried out in the presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1 - about 2 mol per 1 mol of compound (9)). Alternatively, compound (9) may be reacted with 1,1'-carbonyldiimidazole (CDI) (The amount of CDI to be used is generally about 1 - about 3 mol per 1 mol of compound (9)), and then reacted with the corresponding amine.

When R^6 is an alkyl group, cycloalkyl group, aryl group, heterocyclic group etc. having a functional group, it may be appropriately protected with a protecting group and, after ureation, deprotected. When the alkyl group, cycloalkyl group, aryl group, heterocyclic group and the like have substituents, they may be converted, after ureation, to other functional groups by known methods. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

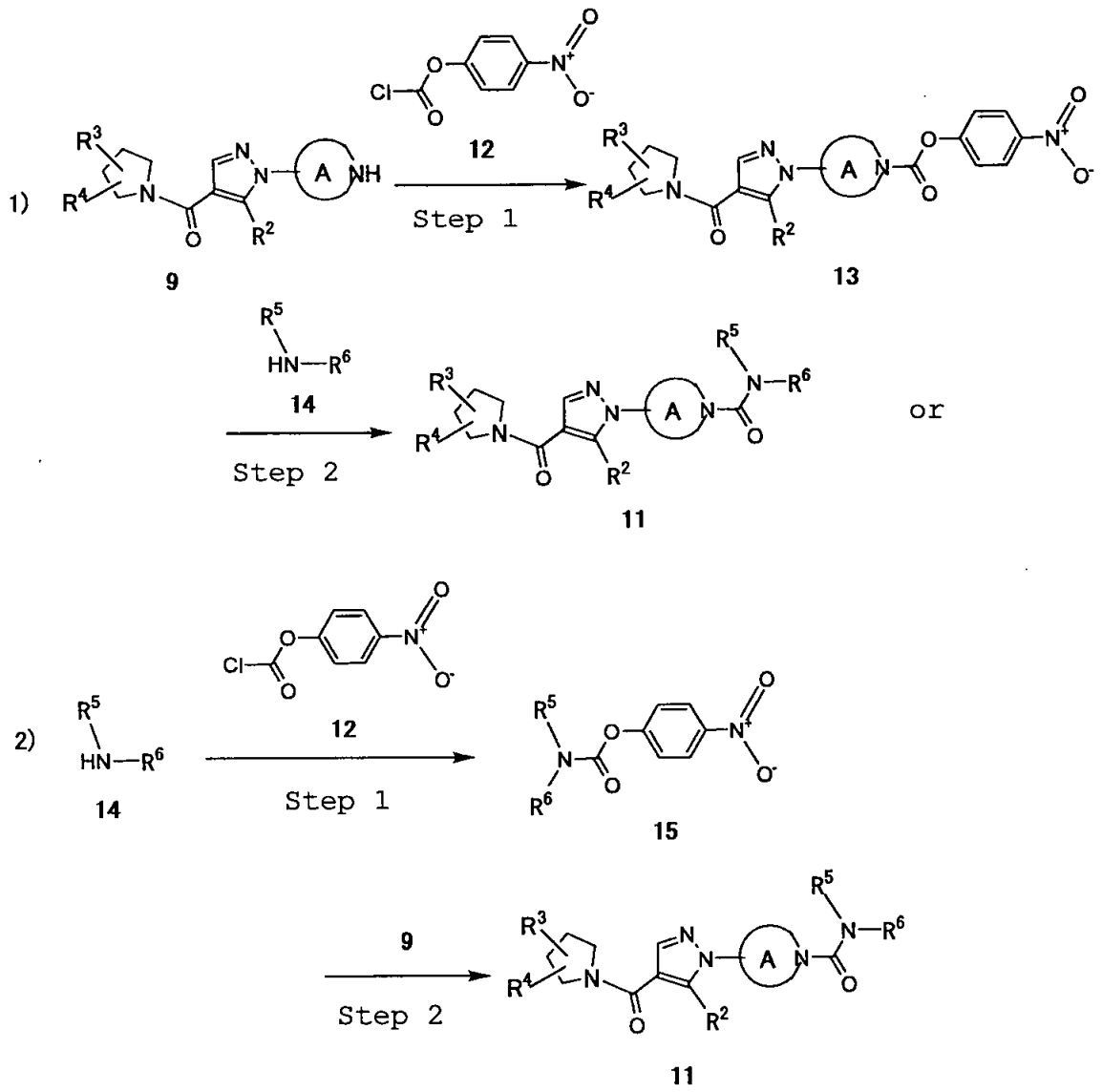
2) When R^6 is hydrogen

Compound (11) is obtained by reacting compound (9) with cyanate in a solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, water, acetic acid, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of cyanate to be used is generally about 1 - about 10 mol, per 1 mol of compound (9). When amine (9) is a salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is

generally about 1 - about 2 mol, per 1 mol of compound (9)).

Production Method 3

The compound of the present invention [1'] wherein -X- is $-N(R^1)-$ and R^1 is $-CONR^5R^6$ can be produced by the following steps.



wherein each symbol is as defined above.

Step 1: Phenylcarbamation step

Compound (13) is obtained by reacting compound (9) with 4-nitrophenyl chloroformate (12) in a solvent in the presence of a base. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be

mentioned. As the base, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of 4-nitrophenyl chloroformate (12) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). The amount of the base to be used is generally about 1 - about 2 mol, per 1 mol of compound (9). When amine (9) is a salt, the reaction is carried out with a base in an amount of about 2 - about 4 mol per 1 mol of compound (9).

Step 2: Ureation step

Compound (11) is obtained by reacting phenylcarbamate intermediate (13) with amine (14) in a solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N-methylpyrrolidone, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 150°C. The reaction time is generally 1 hr to 24 hr. The amount of amine (14) to be used is generally about 1 - about 3 mol per 1 mol of compound (9). When amine (14) is a salt, the reaction is carried out in the presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1 - about 3 mol per 1 mol of compound (13)).

As a different method, as shown in the formula 2), compound (15) is obtained in Step 1 by reacting amine (14) with 4-nitrophenyl chloroformate (12) in a solvent, and compound (15) is reacted with amine (9) in Step 2 to give compound (11).

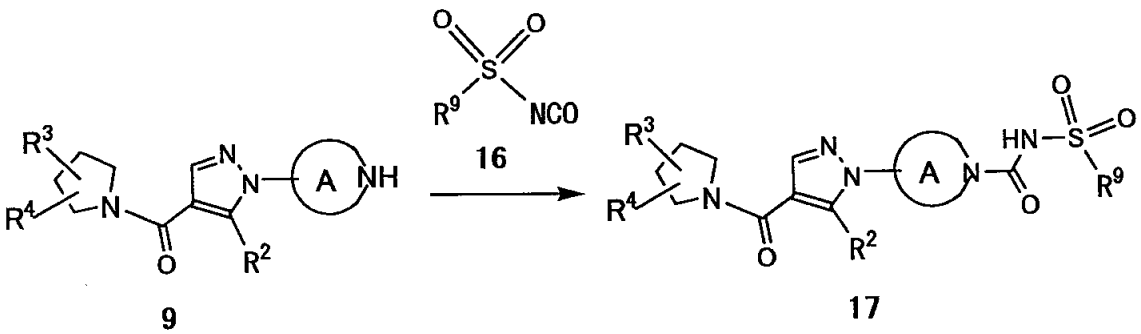
Moreover, other chloroformate or 1,1'-carbonyldiimidazole (CDI) may be used instead of 4-nitrophenyl chloroformate (12).

When R^5 and/or R^6 are/is alkyl group, cycloalkyl group, aryl group, heterocyclic group etc. having a functional group, they are appropriately protected with a protecting group and, after ureation, deprotected. When the alkyl group, cycloalkyl

group, aryl group, heterocyclic group and the like have substituent(s), they can be converted to other functional groups after ureation by a known method. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 4

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$, R^1 is $-CONR^5R^6$ wherein R^5 is a hydrogen atom, and R^6=$-S(=O)_2R^9$) can be produced by the following Steps.



wherein each symbol is as defined above.

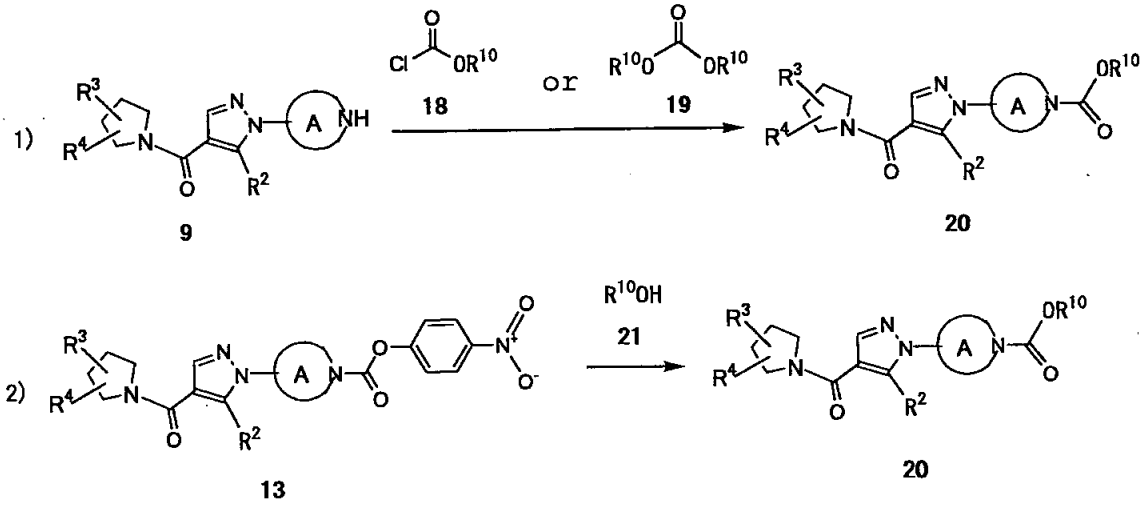
Step 1: Sulfonylureation step

Compound (17) is obtained by reacting compound (9) with sulfonylisocyanate (16) in a solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of sulfonylisocyanate (16) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). When amine (9) is a salt, the reaction is carried out in the presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1 - about 2 mol per 1

mol of compound (9)).

Production Method 5

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is $-COOR^{10}$ can be produced by the following Steps.



wherein each symbol is as defined above.

Step 1: Carbamation step

Compound (20) is obtained by reacting compound (9) with chlorocarbonate (18) or carbonate (19) in the presence of a base, in a solvent or without solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. As the base, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. The reaction temperature is generally 0°C to 150°C. The reaction time is generally 1 hr to 24 hr. The amount of chlorocarbonate (18) or carbonate (19) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). The amount of the base to be used is generally about 1 - about 2 mol per 1 mol of compound (9). When amine (9) is a salt, the reaction is carried out with a base in an amount of about 2 - about 4 mol per 1 mol of compound (9).

When R^{10} is alkyl group, cycloalkyl group, aryl group, heterocyclic group etc. having a functional group, they are

appropriately protected with a protecting group and, after carbamation, deprotected. When the alkyl group, cycloalkyl group, aryl group, heterocyclic group and the like have substituent(s), they can be converted to other functional groups after carbamation by a known method. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

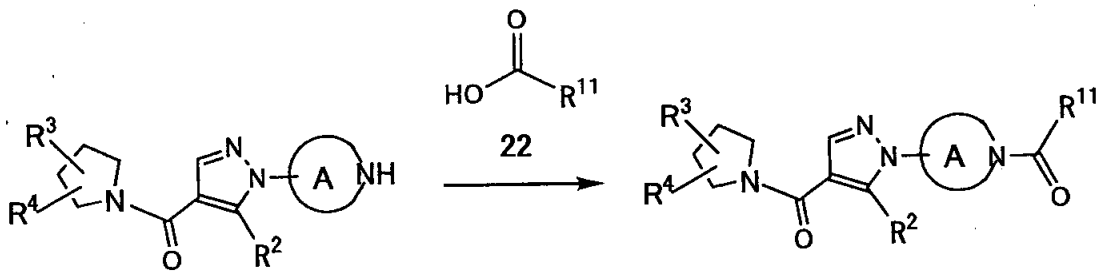
As a different method, as shown in the formula 2), phenylcarbamate intermediate (13) obtained in Production Method 3, Step 1 is reacted with alcohol (21) in a solvent, in the presence of a base to give Compound (20). As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N-methylpyrrolidone, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. As the base, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. The reaction temperature is generally 0°C to 150°C. The reaction time is generally 1 hr to 24 hr. The amount of alcohol (21) to be used is generally about 1 - about 3 mol per 1 mol of phenylcarbamate intermediate (13). The amount of the base to be used is generally about 1 - about 2 mol per 1 mol of phenylcarbamate intermediate (13).

When R^{10} is alkyl group, cycloalkyl group, aryl group, heterocyclic group etc. having a functional group, they are appropriately protected with a protecting group and, after carbamation, deprotected. When the alkyl group, cycloalkyl group, aryl group, heterocyclic group and the like have substituent(s), they can be converted to other functional

groups after carbamation by a known method. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 6

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$, and R^1 is $-COR^{11}$ can be produced by the following Steps.



wherein each symbol is as defined above.

Step 1: Amidation step

Compound (23) is obtained by reacting compound (9) with carboxylic acid (22) in a solvent in the presence of a condensing agent and an additive. As the condensing agent, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), diisopropylcarbodiimide, 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA) and the like can be mentioned. As the additive, 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinic imide (HOSu), 4-dimethylaminopyridine (DMAP) and the like can be mentioned. As the solvent, dichloromethane, chloroform, acetonitrile, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of carboxylic acid (22) to be used is

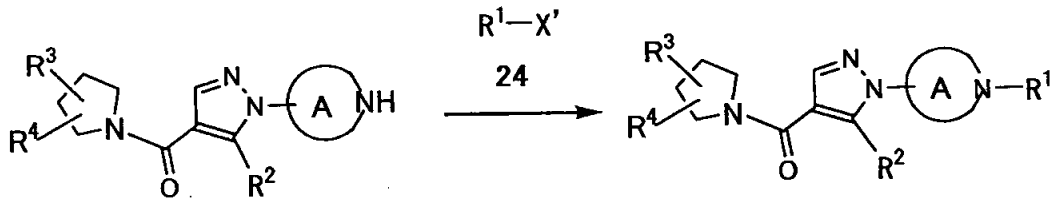
generally about 1 - about 1.5 mol per 1 mol of compound (9). In addition, the amount of the condensing agent and the additive to be used is generally about 1 - about 1.5 mol and about 1 - about 1.5 mol, respectively, per 1 mol of compound (9). When compound (9) is a salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like. Moreover, carboxylic acid (22) may be led to an acid halide or a mixed acid anhydride and reacted with compound (9) in the presence of a base. The amount of the base to be used is generally about 1 - about 1.5 mol per 1 mol of compound (9).

When R^{11} is alkyl group, cycloalkyl group, aryl group, heterocyclic group etc. having a functional group, they are appropriately protected with a protecting group and, after amidation, deprotected. When the alkyl group, cycloalkyl group, aryl group, heterocyclic group and the like have substituent(s), they can be converted to other functional groups after amidation by a known method.

For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 7

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is C_{1-6} alkyl group or cycloalkyl group can be produced by the following Steps.



9 25

wherein X' is a halogen atom and other symbols are as defined above.

Step 1: N-alkylation step

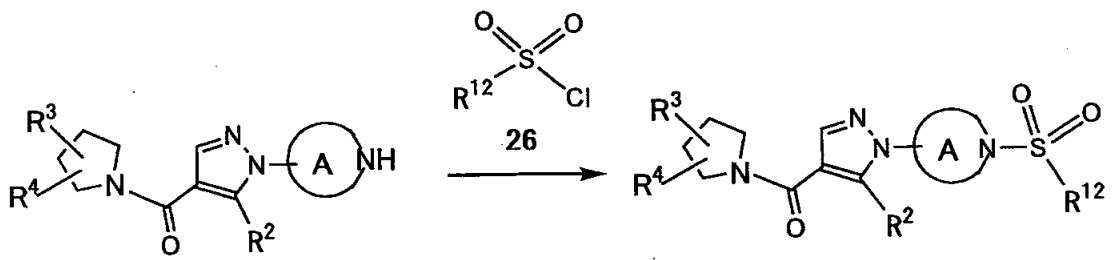
Compound (25) is obtained by reacting compound (9) with alkylhalide (24) in a solvent in the presence of a base. As the base, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium hydride, potassium hydride, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. As the solvent, acetonitrile, acetone, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 30 min to 24 hr. The amount of alkylhalide (24) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). The amount of the base to be used is generally about 1 - about 2 mol per 1 mol of compound (9). When amine (9) is a salt, the reaction is carried out with a base in an amount of about 2 - about 4 mol per 1 mol of compound (9). It is also possible to perform reductive amination of compound (9) with the corresponding aldehyde, ketone, or an equivalent thereof.

When R^1 is alkyl group having a functional group, it is appropriately protected with a protecting group and, after N-alkylation, deprotected. When the alkyl group has substituent(s), it can be converted to other functional group after N-alkylation by a known method. For example, conversion

from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 8

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is $-S(=O)_2R^{12}$ can be produced by the following Steps.



wherein each symbol is as defined above.

Step 1: Sulfonylation step

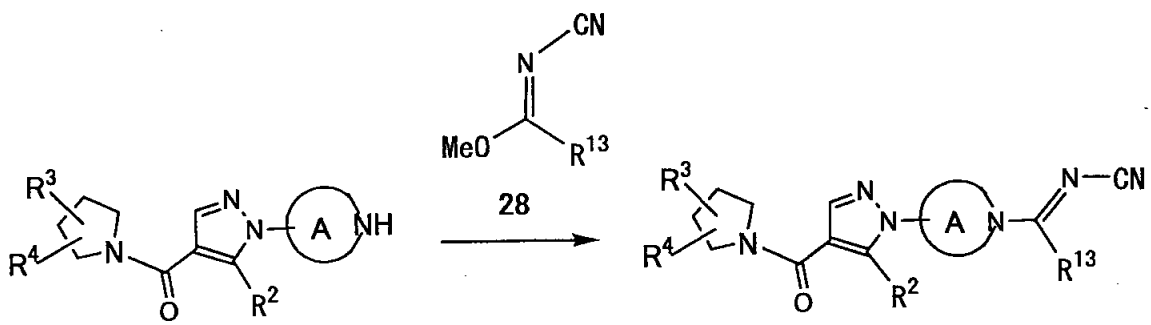
Compound (27) can be obtained by reacting compound (9) with sulfonyl chloride (26) in a solvent in the presence of a base. As the base, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium hydride, potassium hydride, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. As the solvent, acetonitrile, acetone, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 30 min to 24 hr. The amount of sulfonyl chloride (26) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). The amount of the base to be used is generally about 1 - about 2 mol per 1 mol of compound (9). When amine

(9) is a salt, the reaction is carried out with a base in an amount of about 2 - about 4 mol per 1 mol of compound (9). In addition, compound (9) may be reacted with the corresponding sulfonic anhydride.

When R^{12} is alkyl group having a functional group, it is appropriately protected with a protecting group and, after sulfonylation, deprotected. When the alkyl group has substituent(s), it can be converted to other functional group after sulfonylation by a known method. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 9

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is $-C(=NCN)R^{13}$ can be produced by the following Steps.



wherein each symbol is as defined above.

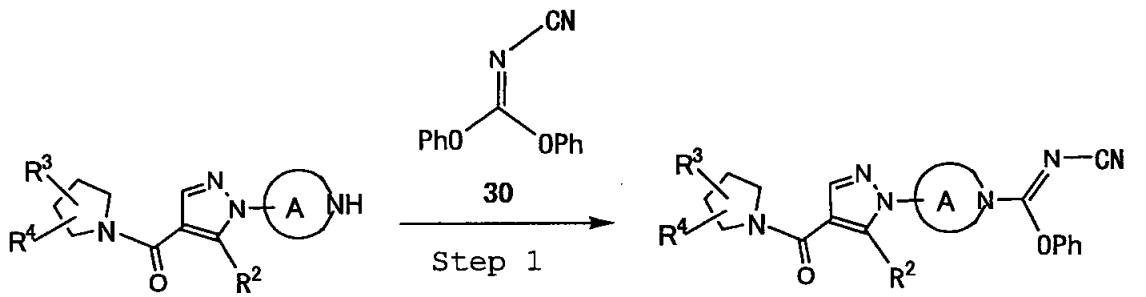
Step 1: Production step of N-cyanoamidine

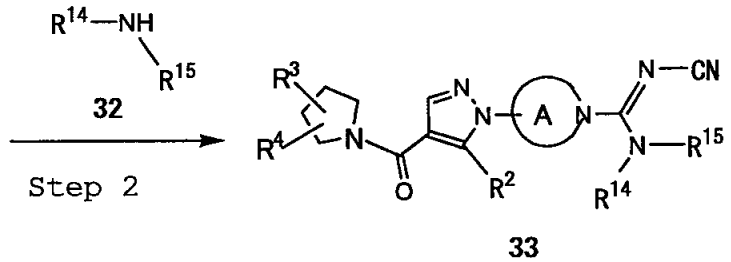
Compound (29) is obtained by reacting compound (9) with N-cyanoimidoacetate (28) in a solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction

temperature is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of N-cyanoimidoacetate (28) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). When amine (9) is a salt, the reaction is carried out in the presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1 - about 2 mol per 1 mol of compound (9)).

Production Method 10

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is $-C(=NCN)NR^{14}R^{15}$ can be produced by the following Steps.





wherein Ph is a phenyl group and other symbols are as defined above.

Step 1

Compound (31) is obtained by reacting compound (9) with diphenyl N-cyanocarbonimidate (30) in a solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction

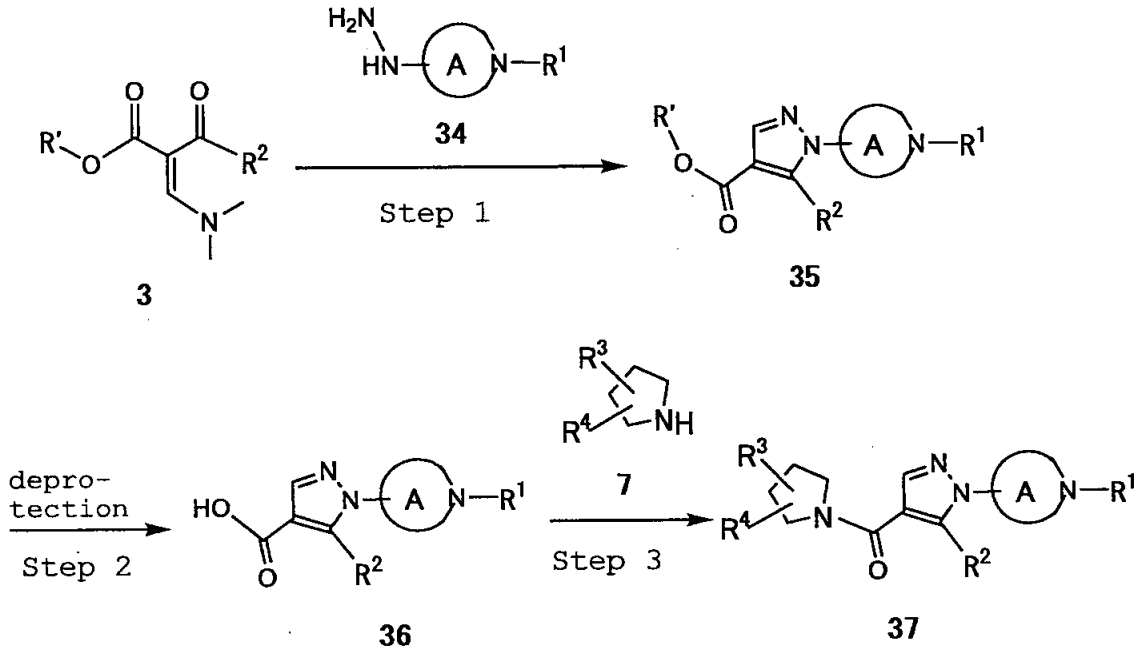
time is generally 1 hr to 24 hr. The amount of diphenyl N-cyanocarbonimidate (30) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). When amine (9) is a salt, the reaction is carried out in the presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1 - about 2 mol per 1 mol of compound (9)).

Step 2: Production step of N-cyanoguanidine

Compound (33) is obtained by reacting compound (31) with amine (32) in a solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N-methylpyrrolidone, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 150°C. The reaction time is generally 1 hr to 24 hr. The amount of amine (32) to be used is generally about 1 - about 5 mol per 1 mol of compound (31). When amine (32) is a salt, the reaction is carried out in the presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1 - about 20 mol per 1 mol of compound (31)).

Production Method 11

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is an aryl group or 5-membered or 6-membered unsaturated monocyclic heterocyclic group can be produced by the following Steps.



wherein each symbol is as defined above.

Step 1: Step for constructing pyrazole ring from hydrazine (34) and compound (3)

Compound (35) is obtained by reacting hydrazine (34) synthesized by a known method with compound (3) obtained in Production Method 1, Step 1, in a solvent. As the solvent, methanol, ethanol, n-propanol, n-butanol, isopropanol, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 250°C. The reaction time is generally 1 hr to 24 hr. The amount of hydrazine (34) to be used is generally about 1.5 - about 3 mol per 1 mol of compound (3). When hydrazine (34) is a salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1.5 - about 3 mol per 1 mol of compound (3)).

Step 2: Deprotection step of carboxyl-protecting group R'

Compound (36) is obtained by eliminating carboxyl-protecting group R' by a known method.

Step 3: Amidation step

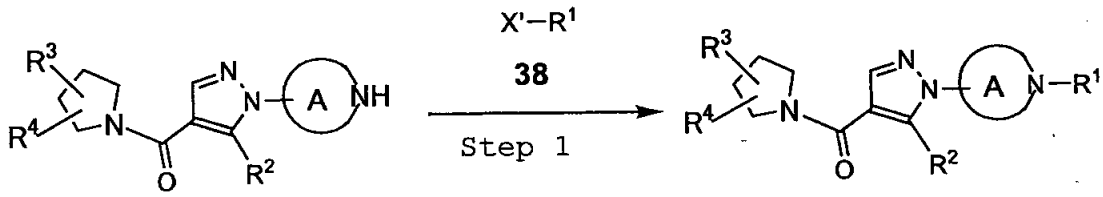
Compound (37) is obtained by reacting compound (36) with amine (7) in a solvent in the presence of a condensing agent and an additive. As the condensing agent, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), diisopropylcarbodiimide, 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA) and the like can be mentioned. As the additive, 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinic imide (HOSu), 4-dimethylaminopyridine and the like can be mentioned. As the solvent, dichloromethane, chloroform, acetonitrile, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of amine (7) to be used is generally about 1 - about 1.5 mol per 1 mol of compound (36). In addition, the amount of the condensing agent and the additive to be used is generally about 1- about 1.5 mol and about 1- about 1.5 mol, respectively, per 1 mol of compound (36). When amine (7) is a salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like. In addition, carboxylic acid (36) may be led to an acid halide and then reacted with amine (7) in the presence of a base. The amount of the base to be used is generally about 1 - about 1.5 mol per 1 mol of compound (36).

When R^1 is aryl group or a 5-membered or 6-membered unsaturated monocyclic heterocyclic group having a functional group, it is appropriately protected with a protecting group and thereafter deprotected. When the aryl group or 5-membered

or 6-membered unsaturated monocyclic heterocyclic group has substituent(s), it can be converted to other functional group by a known method after this step. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 12

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is an aryl group or 5-membered or 6-membered unsaturated monocyclic heterocyclic group can be produced by the following Steps.



9 39

wherein each symbol is as defined above.

Step 1: Palladium catalyzed Buchwald/Hartwig type amination step

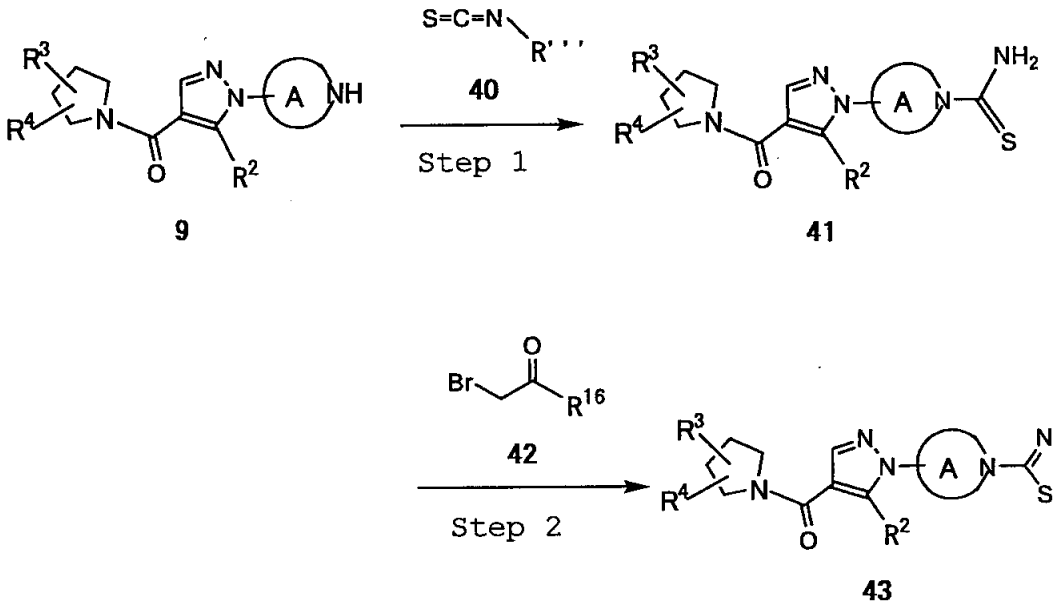
Compound (39) is obtained by reacting compound (9) obtained in Production Method 1 and aromatic halide (38) in a solvent in the presence of a palladium catalyst and a base. As the palladium catalyst, a mixture of palladium acetate and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, bis(diphenylphosphino)ferrocene palladium (II) dichloride, tris(dibenzylideneacetone) dipalladium and the like can be mentioned. As the base, tripotassium phosphate (K_3PO_4), sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, potassium tert-butoxide and the like can be mentioned. As the solvent, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane, benzene, toluene, xylene, tert-butanol, and a mixed solvent thereof and

the like can be mentioned. The reaction temperature is generally 20°C to 250°C. The reaction time is generally 1 hr to 24 hr. The amount of aromatic halide (38) to be used is generally about 1 - about 1.5 mol per 1 mol of compound (9). The amount of the palladium catalyst and the base to be used is generally about 0.01- about 0.1 mol and about 1- about 2 mol, respectively, per 1 mol of compound (9).

When R^1 is an aryl group or a 5-membered or 6-membered unsaturated monocyclic heterocyclic group having a functional group, it is appropriately protected with a protecting group and thereafter deprotected. When the aryl group or a 5-membered or 6-membered unsaturated monocyclic heterocyclic group has substituent(s), it can be converted to other functional group after this step by a known method. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 13

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is an aryl group or 5-membered or 6-membered unsaturated monocyclic heterocyclic group can be produced by the following Steps.



wherein R"' is a substituent (e.g., ethoxycarbonyl group, benzoyl group, 9-fluorenylmethoxycarbonyl group and the like) on nitrogen atom, and other symbols are as defined above.

Step 1: Thioureation step

Compound (41) is obtained by reacting compound (9) obtained in Production Method 1 with isothiocyanate (40) in a solvent and eliminating the substituent (R"') on the nitrogen atom by a known method. As isothiocyanate (40), ethoxycarbonylisothiocyanate, benzoylisothiocyanate, 9-fluorenylmethoxycarbonylisothiocyanate and the like can be mentioned. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of isothiocyanate (40) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). It is possible to react compound (9) with thiophosgene (the amount of thiophosgene to be used is generally about 1 - about 1.5 mol per 1 mol of compound (9)), followed by an ammonia treatment.

Step 2: Step for constructing thiazole ring

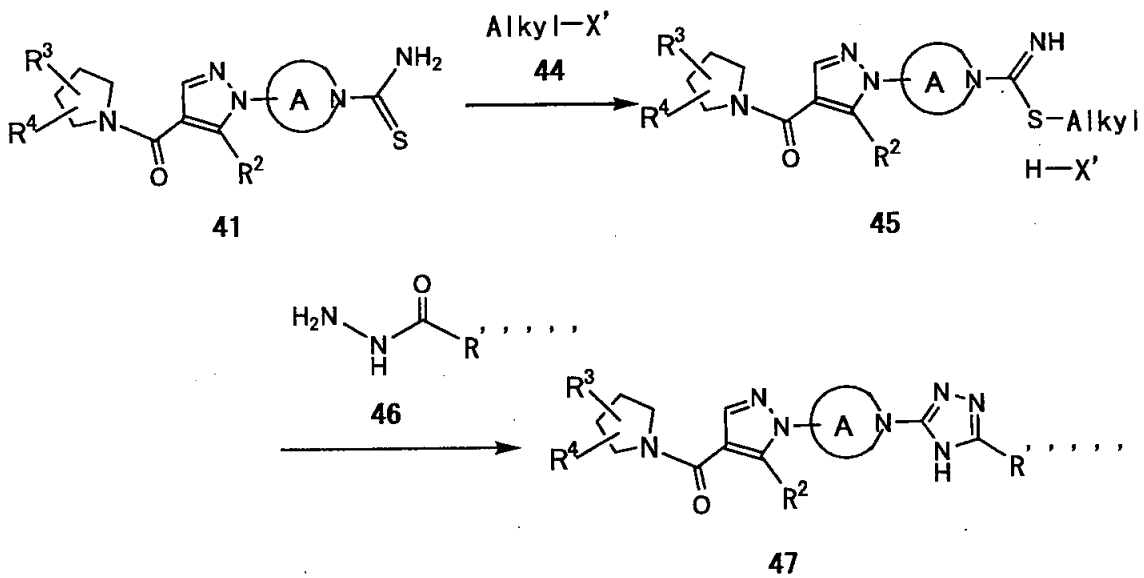
Compound (43) is obtained by reacting compound (41) with

halomethylketone (42) in a solvent. As the solvent, methanol, ethanol, n-propanol, n-butanol, isopropanol, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 250°C. The reaction time is generally 1 hr to 24 hr. The amount of halomethylketone (42) to be used is generally about 1 - about 1.5 mol per 1 mol of compound (41).

A thiazolyl group having a functional group can be appropriately protected with a protecting group and thereafter deprotected. When the thiazolyl group has substituent(s), it can be converted to other functional group after this step by a known method. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 14

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is a 5-membered or 6-membered unsaturated monocyclic heterocyclic group can be produced by the following Steps.



wherein X' is a halogen atom, Alkyl is a C_{1-6} alkyl group, R''''' is a carboxyl group, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from halogen atom and hydroxyl group), or a cycloalkyl group and other symbols are as defined above.

Step 1

Isothiourea hydrohalide (45) is obtained by reacting compound (41) obtained in Production Method 13, Step 1 with alkylhalide (44) in a solvent. As the solvent, acetonitrile, acetone, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 30 min to 24 hr. The amount of alkylhalide (44) to be used is generally about 1 - about 2 mol per 1 mol of compound (41).

Step 2: Step for constructing triazole ring from isothiourea and hydrazide

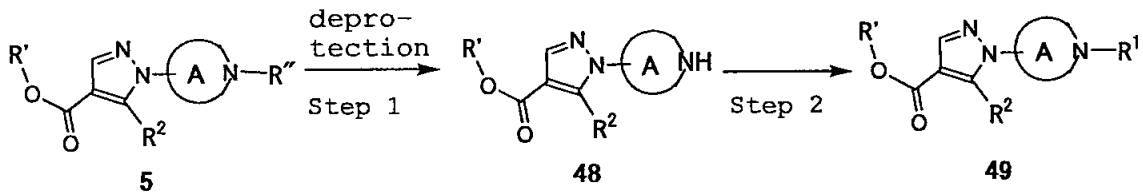
Compound (47) can be obtained by reacting isothiourea hydrohalide (45) with hydrazide (46) synthesized by a known method in a solvent in the presence of a base. As the solvent, methanol, ethanol, n-propanol, isopropanol, n-butanol, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, 1,2-dichloroethane, chloroform, benzene, chlorobenzene, O-dichlorobenzene, toluene, xylene, pyridine, 2,6-lutidine, 2,4,6-collidine, acetic acid, water, and a mixed solvent thereof and the like can be mentioned. As the base, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydride, potassium hydride, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. The reaction temperature is generally 20°C to 250°C. The

reaction time is generally 30 min to 24 hr. The amount of hydrazide (46) to be used is generally about 1 - about 2 mol per 1 mol of isothiourea hydrohalide (45). The amount of the base to be used is generally about 1 - about 2 mol per 1 mol of isothiourea hydrohalide (45). When hydrazide (46) is a salt, the reaction is carried out with a base in an amount of about 2 - about 4 mol per 1 mol of isothiourea hydrohalide (45).

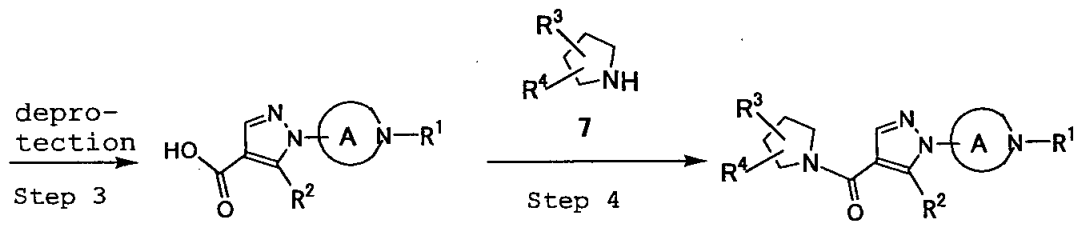
A triazolyl group having a functional group can be appropriately protected with a protecting group and thereafter deprotected. When the triazolyl group has substituent(s), the substituent(s) can be converted by a known method to other functional group after this step. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 15

In the compound [1'] of the present invention, a compound wherein -X- is -N(R^1)- can be produced by the following Steps.



5 48 49



50 51

wherein each symbol is as defined above.

Step 1: Deprotection step of amino protecting group

Compound (48) is obtained by eliminating the amino protecting group R″ of compound (5) obtained in Production

Method 1, Step 2.

Step 2: Introduction of R^1

Compound (49) is obtained by introducing R^1 into compound (48) by a method similar to Production Methods 2 to 10, and Production Methods 12 to 14.

Step 3: Deprotection step of carboxyl-protecting group

Compound (50) is obtained by eliminating the carboxyl-protecting group R' of compound (49) by a known method.

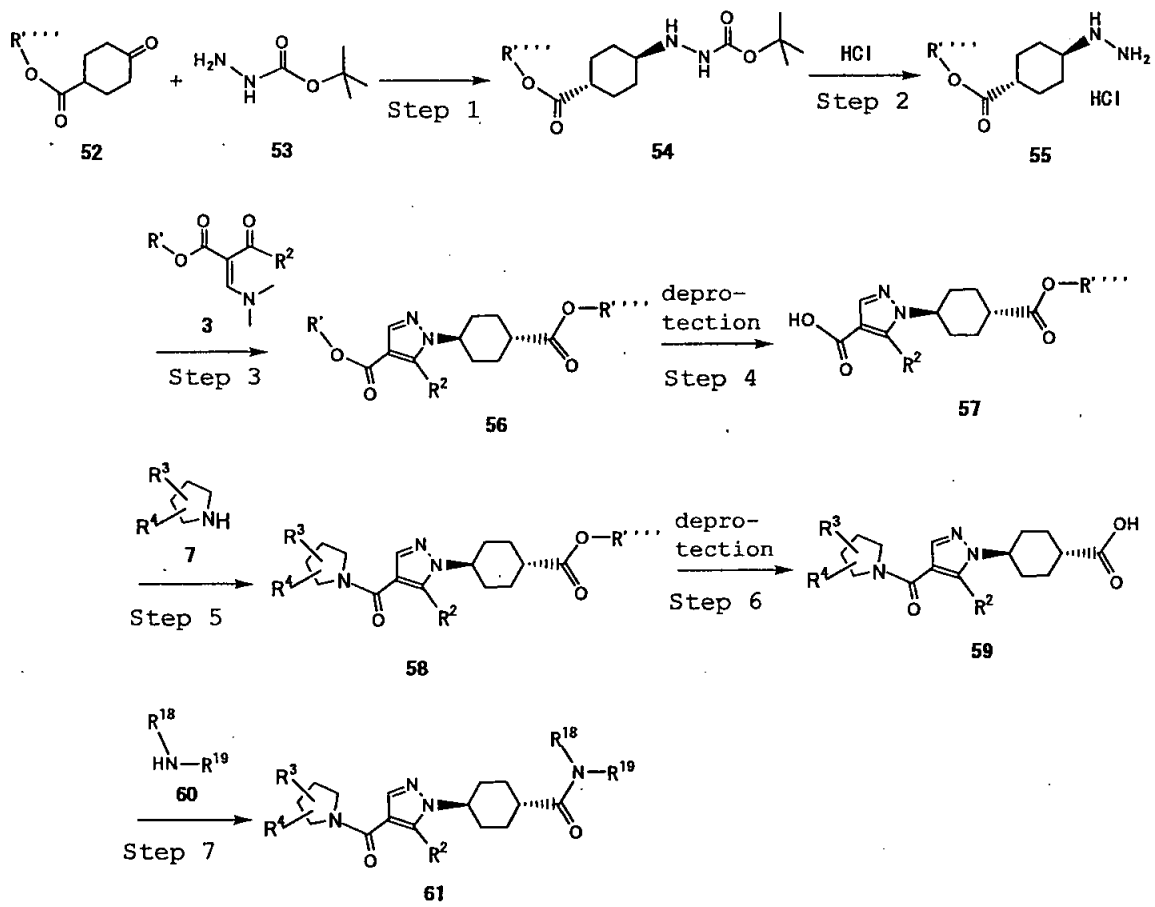
Step 4: Amidation step

Compound (51) is obtained by reacting compound (50) with amine (7) in a solvent in the presence of a condensing agent and an additive. As the condensing agent, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), diisopropylcarbodiimide, 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA) and the like can be mentioned. As the additive, 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinic imide (HOSu), 4-dimethylaminopyridine (DMAP) and the like can be mentioned. As the solvent, dichloromethane, chloroform, tetrahydrofuran, acetonitrile, 1,4-dioxane, N,N-dimethylformamide, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of amine (7) to be used is generally about 1 - about 1.5 mol per 1 mol of compound (50). In addition, the amount of the condensing agent and the additive to be used is generally about 1- about 1.5 mol and about 1- about 1.5 mol, respectively, per 1 mol of compound (50). When amine (7) is a salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1 - about 1.5 mol per 1 mol of compound (50)).

R^1 having a functional group is appropriately protected with a protecting group and thereafter deprotected. When R^1 has substituent(s), it can be converted to other functional group after this step by a known method. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 16

In the compound [1'] of the present invention, a compound wherein -X- is $-C(R^7R^8)-$ can be produced by the following Steps.



wherein each symbol is as defined above where R"" is a carboxy-protecting group (here, the carboxy-protecting group means those generally used in the field of organic synthesis chemistry, such as methyl group, ethyl group, propyl group,

tert-butyl group, benzyl group, p-methoxybenzyl group and the like, which is in the form of esters capable of being easily led to carboxylic acid by hydrolysis, catalytic hydrogenation and the like)

Step 1: Reductive alkylation

Compound (54) is obtained by reacting ketone (52) with tert-butyl carbazate (53) in a solvent in the presence of a reducing agent. As the reducing agent, sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, borane complex and the like can be mentioned. As the solvent, methanol, ethanol, n-propanol, n-butanol, isopropanol, dichloromethane, chloroform, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, benzene, toluene, xylene, acetic acid, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of the reducing agent to be used is generally about 2- about 5 mol, per 1 mol of compound (52).

Step 2: de-BOC (tert-butoxycarbonyl group)

Compound (54) is reacted with 4N hydrochloric acid ethyl acetate solution, or 4N hydrochloric acid 1,4-dioxane solution to give hydrazine hydrochloride (55). In addition, after de-BOC by the action of trifluoroacetic acid in a solvent, it may be converted to hydrochloride. As the solvent, dichloromethane, chloroform and the like can be mentioned.

Step 3: Step for constructing pyrazole ring from hydrazine hydrochloride (55) and compound (3)

Compound (56) is obtained by reacting hydrazine hydrochloride (55) with compound (3) in a solvent in the presence of a base. As the solvent, methanol, ethanol, n-propanol, n-butanol, isopropanol, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. As the base, sodium carbonate, potassium carbonate, sodium hydrogen

carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. The reaction temperature is generally 20°C to 250°C. The reaction time is generally 1 hr to 24 hr. The amount of hydrazine hydrochloride (55) to be used is generally about 1 - about 2 mol per 1 mol of compound (3). The amount of the base to be used is generally about 1 - about 2 mol per 1 mol of compound (3).

Step 4: Deprotection step of carboxyl-protecting group

Compound (57) is obtained by eliminating carboxyl-protecting group R' of compound (56) by a known method.

Step 5: Amidation step

Compound (58) is obtained by reacting compound (57) with amine (7) in a solvent in the presence of a condensing agent and an additive. As the condensing agent, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), diisopropylcarbodiimide, 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA) and the like can be mentioned. As the additive, 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinic imide (HOSu), 4-dimethylaminopyridine (DMAP) and the like can be mentioned. As the solvent, dichloromethane, chloroform, acetonitrile, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of amine (7) to be used is generally about 1 - about 1.5 mol per 1 mol of compound (57). In addition, the amount of the condensing agent and the additive to be used is generally about 1 - about 1.5 mol and about 1 - about 1.5 mol, respectively, per 1 mol of compound (57). When amine (7) is a salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate,

potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like. In addition, carboxylic acid (57) may be led to an acid halide or a mixed acid anhydride and reacted with amine (7) in the presence of a base. The amount of the base to be used is generally about 1 - about 1.5 mol per 1 mol of compound (57).

Step 6: Deprotection step of carboxyl-protecting group

Carboxylic acid (59) is obtained by eliminating the carboxyl-protecting group R"" of compound (58) by a known method.

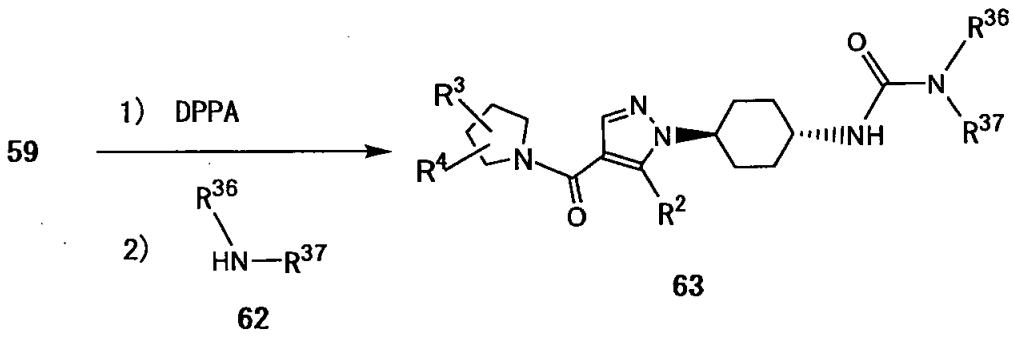
Step 7: Amidation step

Compound (61) is obtained by reacting carboxylic acid (59) with amine (60) in a solvent in the presence of a condensing agent and an additive. As the condensing agent, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), diisopropylcarbodiimide, 1,1'-carbonyldiimidazole (CDI) or, diphenylphosphoryl azide (DPPA) and the like can be mentioned. As the additive, 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinic imide (HOSu), 4-dimethylaminopyridine (DMAP) and the like can be mentioned. As the solvent, dichloromethane, chloroform, acetonitrile, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of amine (60) to be used is generally about 1 - about 1.5 mol per 1 mol of carboxylic acid (59). In addition, the amount of the condensing agent and the additive to be used is generally about 1 - about 1.5 mol and about 1 - about 1.5 mol, respectively, per 1 mol of compound (59). When amine (60) is a salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, sodium acetate, potassium acetate, sodium hydroxide,

potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like. Moreover, carboxylic acid (59) may be led to an acid halide or a mixed acid anhydride and reacted with amine (60) in the presence of a base. The amount of the base to be used is generally about 1 - about 1.5 mol per 1 mol of carboxylic acid (59).

Production Method 17

In the compound [1'] of the present invention, a compound wherein -X- is $-C(R^7R^8)-$ can be produced by the following Steps.



Step 1

wherein each symbol is as defined above.

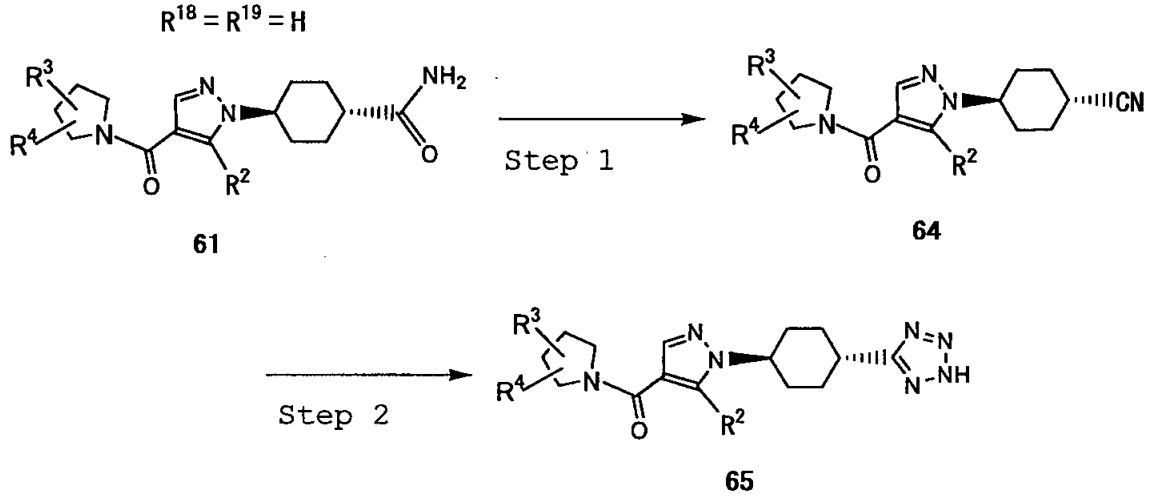
Step 1: Ureation step

Carboxylic acid (59) is reacted with diphenylphosphoryl azide (DPPA) in a solvent in the presence of a base to lead to isocyanate, which is reacted with amine (62) to give urea (63). As the solvent, dichloromethane, chloroform, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, benzene, toluene, xylene and the like can be mentioned. As the base, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. The reaction temperature for the step to give isocyanate is generally 20°C to 150°C, and the step to give urea is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr for both steps. The amount of DPPA to be used is generally about 1- about 2 mol per 1 mol of carboxylic acid (59). The amount of the base to be used is generally about 1 - about 2 mol per 1 mol of carboxylic acid (59). The amount of amine (62) to be used is generally about 1 - about 5 mol per 1

mol of carboxylic acid (59).

Production Method 18

In the compound [1'] of the present invention, a compound wherein -X- is $-C(R^7R^8)-$ can be produced by the following Steps.



61 64 65

wherein each symbol is as defined above.

Step 1: Cyanation step

Nitrile (64) is obtained by reacting amide (61) with a dehydrating agent in a solvent in the presence of a base. As the dehydrating agent, trifluoromethanesulfonic acid anhydride, p-toluenesulfonyl chloride, trichloroacetyl chloride, trifluoroacetic acid anhydride, phosphorus oxychloride, thionyl chloride and the like can be mentioned. As the base, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. As the solvent, dichloromethane, chloroform, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, pyridine, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of the dehydrating agent to be used is generally about 1 - about 2 mol per 1 mol of amide (61). The amount of the base to be used is generally about 1 - about 2 mol, per 1 mol of amide (61).

Step 2: Step for constructing tetrazole ring

Nitrile (64) is reacted in a solvent in the presence of an azidating reagent to give tetrazole (65). As the azidating

reagent, sodium azide, azidotrimethyltin, azidotributyltin, azidotrimethylsilane and the like can be mentioned. As the solvent, dichloromethane, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, N,N-dimethylformamide, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 150°C. The reaction time is generally 1 hr to 24 hr. The amount of the azidating reagent to be used is generally about 1 - about 2 mol per 1 mol of nitrile (64).

The production methods described in this specification are examples of the production methods of the compound of the present invention, and compounds other than those explained above can be produced by combining known conventional methods in the field of organic synthesis chemistry.

Examples

The heterocyclic compounds and production methods thereof of the present invention are explained in detail in the following by referring to Examples, which are not to be construed as limitative.

Example 1

Production of 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine

Step 1

Production of methyl 2-cyclopropylcarbonyl-3-dimethylaminoacrylate

Methyl 3-cyclopropyl-3-oxopropionate (2.0 g) was dissolved in toluene (20 ml). To the obtained solution was added dimethylformamide dimethylacetal (3.0 ml) and the mixture was refluxed for 3 hr. The reaction mixture was allowed to cool and concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (n-hexane:acetone=2:1) to give the title compound as a yellow oil (2.61 g).

Step 2

Production of methyl 1-(1-benzyloxycarbonylpiperidin-4-yl)-5-

cyclopropyl-1H-pyrazole-4-carboxylate

Methyl 2-cyclopropylcarbonyl-3-dimethylaminoacrylate (1.0 g) produced in the previous step and benzyl 4-hydrazinopiperidine-1-carboxylate hydrochloride (1.49 g) synthesized by a known method were suspended in ethanol. To the obtained suspension was added triethylamine (0.78 ml) and the mixture was refluxed for 3.5 hr. Water was added to the reaction mixture and the mixture was extracted with diethyl ether. The diethyl ether layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=2.5:1) to give the title compound as a yellow oil (1.58 g).

Step 3

Production of 1-(1-benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

Methyl 1-(1-benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carboxylate (1.58 g) produced in the previous step was dissolved in tetrahydrofuran (5 ml), methanol (5 ml) and water (10 ml), lithium hydroxide monohydrate (834 mg) was added and the mixture was stirred at 50°C for 6 hr. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, acidified with 2N hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. To the obtained residue were added diethyl ether and n-hexane, and the precipitated solid was collected by filtration, and dried to give the title compound as a white amorphous solid (1.27 g).

Step 4

Production of 1-[1-(1-benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine

1-(1-Benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid (800 mg) produced in the previous step, 1-hydroxybenzotriazole (332 mg) and 1-ethyl-3-(3-

dimethylaminopropyl)-carbodiimide hydrochloride (498 mg) were dissolved in N,N-dimethylformamide (10 ml), and the mixture was stirred for 15 min. To the obtained solution were added 3-(pyridin-3-yl)pyrrolidine (330 mg) and 4-dimethylaminopyridine (catalytic amount) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=11:1) to give the title compound as a white amorphous solid (1.06 g).

Step 5

Production of 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine

1-[1-(1-Benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine (970 mg) produced in the previous step was dissolved in methanol (12 ml), 10% palladium carbon (50% water content) (200 mg) was added, and the mixture was stirred under a hydrogen atmosphere for 2.5 hr. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by chromatography (neutral alumina) (chloroform:methanol=7:1) to give the title compound as a white amorphous solid (718 mg).

Example 2

Production of 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

Step 1

Production of (S)-3-acetyl-4-isopropyl-5,5-diphenyloxazolidin-2-one

Under an argon atmosphere, (S)-4-isopropyl-5,5-diphenyloxazolidin-2-one (1.56 g) was suspended in

tetrahydrofuran (22 ml), and 1.6M n-butyllithium/n-hexane solution (3.64 ml) was added under ice-cooling. After 10 min, acetyl chloride (0.47 ml) was added, and the mixture was stirred overnight while allowing the mixture to gradually return to room temperature. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was concentrated under reduced pressure. Water was added to the obtained residue and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate solution and water, and dried over anhydrous magnesium sulfate. The ethyl acetate layer was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=4:1) to give the title compound as white crystals (1.69 g).

Step 2

Production of (S)-4-isopropyl-3-[(S)-4-nitro-3-(2-trifluoromethylphenyl)butyryl]-5,5-diphenyloxazolidin-2-one

(S)-3-Acetyl-4-isopropyl-5,5-diphenyloxazolidin-2-one (4.74 g) produced in the previous step was dissolved in dichloromethane (73 ml) under an argon atmosphere, and titanium tetrachloride (3.17 ml) and N,N-diisopropylethylamine (3.06 ml) were added at -78°C. The mixture was gradually warmed to 0°C over 30 min, again cooled to -78°C and a solution of 1-[(E)-2-nitrovinyl]-2-trifluoromethylbenzene (3.50 g) in dichloromethane (27 ml) was added. titanium tetrachloride (3.17 ml) was added and, 2 hr later, saturated aqueous ammonium chloride solution was added to the reaction mixture. The mixture was extracted with ethyl acetate, and the ethyl acetate layer was washed with 1N hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate solution and water, and dried over anhydrous magnesium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=5:1) and crystallized from diethyl ether:n-pentane to give the title

compound as white crystals (2.62 g).

Step 3

Production of (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one

To (S)-4-isopropyl-3-[(S)-4-nitro-3-(2-trifluoromethylphenyl)butyryl]-5,5-diphenyloxazolidin-2-one (2.51 g) produced in the previous step were added ethanol (35 ml) and ethyl acetate (35 ml), and Raney nickel (50% in water) (2.8 g) was added. After stirring overnight under a hydrogen atmosphere, the insoluble material was filtered through celite, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give the title compound as white crystals (850 mg).

Step 4

Production of (S)-3-(2-trifluoromethylphenyl)pyrrolidine

To (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one (803 mg) produced in the previous step was added tetrahydrofuran (7 ml), and aluminum lithium hydride (200 mg) was added. After heating under reflux for 1.5 hr, water (0.2 ml), 4N aqueous sodium hydroxide solution (0.2 ml) and water (0.4 ml) were added under ice-cooling. Anhydrous magnesium sulfate was added, the insoluble material was filtered through celite, and the filtrate was concentrated under reduced pressure to give the title compound as a pale-yellow oil (722 mg).

$[\alpha]^{25}D$=+23.9 (c=0.504, EtOH)

Step 5

Production of 1-[1-(1-benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-(1-Benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid (235 mg) produced in Example 1, Step 3, 1-hydroxybenzotriazole (127 mg) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (159 mg) were dissolved in N,N-dimethylformamide (6 ml), and the mixture was stirred for 15 min. To the obtained solution were added (S)-3-

(2-trifluoromethylphenyl)pyrrolidine (151 mg) produced in the previous step and 4-dimethylaminopyridine (78 mg), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, 1N aqueous potassium hydrogensulfate, saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (ethyl acetate:methanol=40:1) to give the title compound as a white amorphous solid (287 mg).

Step 6

Production of 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

1-[1-(1-Benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (2.0 g) produced in the previous step was dissolved in methanol (14 ml), palladium hydroxide carbon (0.2 g) was added, and the mixture was stirred under a hydrogen atmosphere for 15 hr. The catalyst was filtered off with celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in methanol (6.4 ml), and 4N hydrochloric acid ethyl acetate solution (1.32 ml) was added. The mixture was concentrated under reduced pressure, and crystallized from ethyl acetate+diisopropyl ether to give the title compound as white crystals (1.45 g).

Step 7

(S)-3-(2-trifluoromethylphenyl)pyrrolidine produced in the above-mentioned Step 4 and a hydrochloride thereof can also be produced according to the following Step.

Step 7-1

Production of dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate

Toluene (40 ml) was added to 1-((E)-2-nitrovinyl)-2-trifluoromethylbenzene (4.34 g), and dimethyl malonate (3.4 ml) and 1-(3,5-bis-trifluoromethylphenyl)-3-((1S,2S)-2-dimethylaminocyclohexyl)-thiourea (413 mg) disclosed in WO2005/000803 and J. Am. Chem. Soc., 2005, 127, 119-125 were added under ice-cooling. The mixture was stirred under ice-cooling for 24 hr. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from 2-propanol to give the title compound (5.31 g) as white crystals.

This reaction can also be carried out using catalysts disclosed in J. Am. Chem. Soc., 1999, 121, 10215-10216, J. Am. Chem. Soc., 2005, 127, 9958-9959, J. Am. Chem. Soc., 2006, 128, 1454-1455 and the like, instead of 1-(3,5-bis-trifluoromethylphenyl)-3-((1S,2S)-2-dimethylaminocyclohexyl)-thiourea.

Step 7-2

Production of methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate

Dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate (4.0 g) produced in the previous Step was added to a suspension of Raney nickel (2.0 g) in tetrahydrofuran (10 ml)/methanol (10 ml), and the mixture was stirred under 3.5 atm hydrogen atmosphere at room temperature for 24 hr. Insoluble materials were filtered off through celite. The filtrate and washing were combined and concentrated under reduced pressure. Toluene was added to the residue, and the mixture was washed with 10% aqueous potassium carbonate solution and water, and the organic layer was concentrated under reduced pressure. The residue was crystallized from toluene+n-hexane to give the title compound (2.38 g) as white crystals.

This reaction can also be carried out using palladium carbon instead of Raney nickel with an acid such as acetic acid, tosylic acid, mesylic acid and the like.

Step 7-3

Production of (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one

Methanol (3.8 ml) was added to methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate (1.0 g) produced in the previous Step, 1N-aqueous sodium hydroxide solution (3.8 ml) was further added, and the mixture was stirred at 65°C for 1 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was acidified with 1N-hydrochloric acid under ice-cooling and extracted twice with butyl acetate. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Butyl acetate (10 ml) was newly added to the residue, and the mixture was stirred overnight at 100°C. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from n-hexane to give the title compound (667 mg) as white crystals.

Step 7-4

Production of (S)-3-(2- trifluoromethylphenyl)pyrrolidine hydrochloride

To a solution of (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one (22.9 g) produced in the previous Step in THF (100 ml) was added dropwise 1M lithium aluminium hydride THF solution (100 ml) under an argon atmosphere at 85°C over 1 hr, and the mixture was further stirred at said temperature for 1 hr. After allowing to cool, 50% aqueous Rochelle salt solution was added under ice-cooling, and the mixture was partitioned between water and ethyl acetate. The organic layer was separated and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water, and the organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Ethyl acetate (60 ml) was added to the residue, 4N-hydrochloric acid ethyl acetate solution (37.5 ml) was further added under ice-cooling, and the mixture was stirred at room temperature. The precipitated crystals were collected by filtration to give

the title compound (20.6 g) as white crystals.

$[\alpha]^{25}D$ = +10.3 (c = 0.55, MeOH)

Example 3

Production of 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine (100 mg) produced in Example 1, Step 5 was dissolved in chloroform (2 ml), triethylamine (38 µl) and 2-fluorophenylisocyanate (34 µl) were added, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=11:1) to give the title compound as a white amorphous solid (111 mg).

Example 4

Production of 1-[1-(1-carbamoylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (1.0 g) produced by a method similar to that of Example 1, Step 5 was dissolved in acetic acid (3 ml) and water (6 ml), and an aqueous solution (6 ml) of sodium cyanide (300 mg) was added dropwise at room temperature. The mixture was stirred at room temperature for 6 hr, during which sodium cyanide (750 mg total) was further added. The mixture was extracted with ethyl acetate, and the ethyl acetate layer was washed with 1N hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate solution, water and brine, and dried over anhydrous magnesium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=10:1). Diethyl ether (10 ml) was added, and the mixture was stirred at room temperature for 2 hr. The precipitated solid was collected by filtration

and dried to give the title compound as white crystals (581 mg).

Example 5

Production of 1-{1-[1-(2-carboxyphenylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (703 mg) of Example 2 was suspended in chloroform (7 ml), and triethylamine (0.23 ml) was added. Under ice-cooling, 2-methoxycarbonylphenylisocyanate (292 mg) was added, and the mixture was stirred at room temperature for 2 hr. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=30:1) to give 1-{5-cyclopropyl-1-[1-(2-methoxycarbonylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (992 mg) as a white amorphous solid.

The obtained 1-{5-cyclopropyl-1-[1-(2-methoxycarbonylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (244 mg) was dissolved in tetrahydrofuran (0.4 ml) and methanol (0.2 ml), 4N aqueous sodium hydroxide solution (0.4 ml) was added, and the mixture was stirred at 60°C for 4 hrs. The mixture was concentrated under reduced pressure, and the obtained residue was dissolved in water. Under ice-cooling, the mixture was acidified with 2N hydrochloric acid and extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. n-Hexane was added to the residue to allow crystal precipitation. The obtained crystal was washed with n-hexane and dried under reduced pressure to give the title compound as a white amorphous solid (181 mg).

Example 6

Production of 1-{5-cyclopropyl-1-[1-(2-

hydroxymethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-{5-Cyclopropyl-1-[1-(2-methoxycarbonylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (213 mg) obtained in Example 5 was dissolved in tetrahydrofuran (2 ml) and ethanol (2 ml), and lithium chloride (30 mg) and sodium borohydride (26 mg) were added under ice-cooling. The mixture was stirred overnight at room temperature. The precipitated insoluble material was collected by filtration, and washed with chloroform. The filtrate and washing were combined, and the mixture was washed with water, saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=30:1) to give the title compound as a white amorphous solid (109 mg).

Example 7

Production of 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 5, the title compound was obtained as a white amorphous solid (530 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (1.07 g) of Example 2.

Example 8

Production of 1-{5-cyclopropyl-1-[1-(2-hydroxyethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 5, the title compound was obtained as a white amorphous solid (202 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (206 mg) of Example 2.

Example 9

Production of 1-{5-cyclopropyl-1-[1-(2-hydroxy-1,1-dimethylethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 5, the title compound was obtained as a white amorphous solid (341 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (350 mg) of Example 2.

Example 10

Production of 1-{1-[1-(2-acetylaminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

To 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (5.04 g) of Example 2 was added chloroform (50 ml), N,N-diisopropylethylamine (4.68 ml) and 4-nitrophenyl chloroformate (2.39 g) was added under ice-cooling, and the mixture was stirred at room temperature for 1 hr. The mixture was concentrated under reduced pressure, acidified with 1N hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give the title compound as a pale-yellow amorphous form (5.41 g).

Step 2

Production of 1-{1-[1-(2-acetylaminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-

4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg) produced in the previous step was dissolved in N-methylpyrrolidone (1 ml), and N-(2-aminoethyl)-acetamide (96 µl) was added. The mixture was stirred overnight at 80°C. After allowing to cool, 10% aqueous potassium carbonate solution was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, 1N hydrochloric acid and water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=15:1) to give the title compound as a white amorphous form (65 mg).

Example 11

Production of 1-{1-[1-(2-aminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

1-{5-Cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg) produced in Example 10, Step 1 and t-butyl (2-aminoethyl)carbamate (160 mg) were dissolved in acetonitrile (1 ml), and the mixture was heated under reflux overnight. The mixture was diluted with chloroform, and the mixture was washed with water, saturated aqueous potassium hydrogencarbonate solution, water and brine, and dried over anhydrous magnesium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=10:1). The obtained amorphous solid was dissolved in ethyl acetate (1 ml), and 4N hydrochloric acid ethyl acetate solution (4 ml) was added. The precipitated solid was collected by filtration and dried to give the title compound as a white amorphous solid (111 mg).

Example 12

Production of 1-{5-cyclopropyl-1-[1-(1,1-dioxothiomorpholine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine

1-{5-Cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (250 mg) produced in Example 10, Step 1 and thiomorpholine (0.13 ml) were dissolved in N-methylpyrrolidone (1 ml), and the mixture was stirred overnight at 100°C. After allowing to cool, the mixture was diluted with diethyl ether, washed with water, 5% aqueous potassium carbonate solution and brine, and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:methanol=30:1) to give 1-{5-cyclopropyl-1-[1-(thiomorpholine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine as a white amorphous solid (224 mg). This was dissolved in chloroform (4 ml), and m-chloroperbenzoic acid (319 mg) was added under ice-cooling. The mixture was stirred for 3 hr while allowing it to gradually return to room temperature. Saturated aqueous sodium thiosulfate solution and saturated aqueous sodium hydrogen carbonate solution were added, and the mixture was extracted with chloroform. The chloroform layer was washed with brine and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:methanol=30:1) to give the title compound as a white amorphous solid (198 mg).

Example 13

Production of 1-{5-cyclopropyl-1-[1-(2-dimethylaminoethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 10, the title compound was obtained as a yellow amorphous solid (130 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-

1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 14

Production of 1-{5-cyclopropyl-1-[1-(4-hydroxypiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (176 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 15

Production of 1-{1-[1-(azetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (150 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 16

Production of 1-{5-cyclopropyl-1-[1-(3-hydroxypyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (175 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 17

Production of 1-{5-cyclopropyl-1-[1-(2-piperidin-1-yl-ethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 10, the title compound was obtained as a pale-yellow amorphous solid (170 mg)

from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 18

Production of 1-{5-cyclopropyl-1-[1-(4,4-difluoropiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a pale-yellow amorphous solid (132 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 19

Production of 1-{5-cyclopropyl-1-[1-(3,3-difluoropyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a pale-yellow amorphous solid (152 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 20

Production of 1-{5-cyclopropyl-1-[1-(3-hydroxyazetidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (158 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 21

Production of 1-(5-cyclopropyl-1-{1-[(R)-3-hydroxypyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title

compound was obtained as a white amorphous solid (171 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 22

Production of 1-(5-cyclopropyl-1-{1-[(S)-3-hydroxypyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (172 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 23

Production of 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxy-1-methylethylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a yellow amorphous solid (60 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 24

Production of 1-{5-cyclopropyl-1-[1-(4-hydroxymethylpiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (94 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (150 mg).

Example 25

Production of 1-{1-[1-(4-carboxypiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (65 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (172 mg).

Example 26

Production of 1-{5-cyclopropyl-1-[1-(3-oxopiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (143 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 27

Production of 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxymethylpyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a yellow amorphous solid (150 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 28

Production of 1-{5-cyclopropyl-1-[1-(3-hydroxymethylazetidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a yellow amorphous solid (178 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 29

Production of 1-{5-cyclopropyl-1-[1-(4-methylpiperazine-1-

carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (66 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (150 mg).

Example 30

Production of 1-{5-cyclopropyl-1-[1-(4-isopropylpiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (50 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (150 mg).

Example 31

Production of 1-{1-[1-(4-acetylpiperazine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (56 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (150 mg).

Example 32

Production of 1-(5-cyclopropyl-1-{1-[(R)-3-hydroxypiperidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a yellow amorphous solid (170 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 33

Production of 1-{1-[1-(4-carbamoylpiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (108 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (150 mg).

Example 34

Production of 1-{1-[1-(3-carbamoylazetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (93 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (171 mg).

Example 35

Production of 1-{1-[1-(4-aminopiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 11, the title compound was obtained as a white amorphous solid (302 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (478 mg).

Example 36

Production of 1-{1-[1-(3-aminopyrrolidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 11, the title compound was obtained as a pale-brown yellow amorphous solid (635 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (478 mg).

Example 37

Production of 1-{5-cyclopropyl-1-[1-(piperidin-4-yl-carbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 11, the title compound was obtained as a white amorphous solid (59 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (478 mg).

Example 38

Production of 1-{5-cyclopropyl-1-[1-(4-dimethylaminopiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (74 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (478 mg).

Example 39

Production of 1-{1-[1-(4-acetylaminopiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (100 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (478 mg).

Example 40

Production of 1-{1-[1-(3-acetylaminopyrrolidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (127 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine (478 mg).

Example 41

Production of 1-{5-cyclopropyl-1-[1-(3-dimethylaminopyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 12, the title compound was obtained as a pale-brown yellow amorphous solid (141 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (478 mg).

Example 42

Production of 1-{5-cyclopropyl-1-[1-(1-methylpiperidin-4-yl-carbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (116 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (181 mg).

Example 43

Production of 1-{1-[1-(1-acetylpiperidin-4-yl-carbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (41 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (181 mg).

Example 44

Production of 1-{5-cyclopropyl-1-[1-(4-oxopiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (155 mg) from

1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (540 mg).

Example 45

Production of 1-{1-[1-(3-acetylaminoazetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (68 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (90 mg).

Example 46

Production of 1-{5-cyclopropyl-1-[1-(3-oxopyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (155 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (300 mg).

Example 47

Production of 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of 4-nitrophenyl (2,2,2-trifluoroethyl)carbamate

2,2,2-Trifluoroethylamine (392 mg) was dissolved in chloroform (4 ml), and pyridine (0.35 ml) and 4-nitrophenyl chloroformate (2.39 g) were added under ice-cooling. The mixture was stirred at room temperature for 1 hr. The mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid and water, dried over anhydrous magnesium

sulfate, and concentrated under reduced pressure. Diisopropylether was added to the obtained residue, and the precipitated solid was collected by filtration and dried to give the title compound as a white solid (501 mg).

Step 2

Production of 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

4-Nitrophenyl (2,2,2-trifluoroethyl)carbamate (113 mg) produced in the previous step and 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2 were dissolved in pyridine (1 ml), and the mixture was stirred at 80°C for 2 hr. After allowing to cool, toluene was added and the mixture was concentrated under reduced pressure. 10% Aqueous potassium carbonate solution was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with 10% aqueous potassium carbonate solution, water, 1N hydrochloric acid and water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=15:1) to give the title compound as a pale-yellow amorphous form (162 mg).

Example 48

Production of 1-{5-cyclopropyl-1-[1-(3,3,4,4-tetrafluoropyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 47, the title compound was obtained as a pale-yellow amorphous solid (138 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (468 mg) of Example 2.

Example 49

Production of 1-(5-cyclopropyl-1-{1-[(S)-1-hydroxymethyl-2-methylpropylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-

[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 47, the title compound was obtained as a white amorphous solid (166 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (250 mg) of Example 2.

Example 50

Production of 1-(1-{1-[(S)-1-benzyl-2-hydroxyethylcarbamoyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 47, the title compound was obtained as a white amorphous solid (140 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (300 mg) of Example 2.

Example 51

Production of 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxy-1-phenylethylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 47, the title compound was obtained as a white amorphous solid (170 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (300 mg) of Example 2.

Example 52

Production of 1-(5-cyclopropyl-1-{1-[(S)-1-hydroxymethyl-3-methylbutylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 47, the title compound was obtained as a yellow amorphous solid (256 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (250 mg) of Example 2.

Example 53

Production of 1-{5-cyclopropyl-1-[1-(2-hydroxyphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 47, the title compound was obtained as a white amorphous solid (125 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 54

Production of 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopentylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 47, the title compound was obtained as a white amorphous solid (92 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 55

Production of 1-[1-(1-benzenesulfonylaminocarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Chloroform (3 ml) was added to 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (250 mg) of Example 2, triethylamine (81 µl) and toluenesulfonylisocyanate (78 µl) were added and the mixture was stirred for 2 hr. The mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with chloroform. The chloroform layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=10:1). The obtained solid was recrystallized from ethyl acetate to give the title compound as a pale-yellow solid (40 mg).

Example 56

Production of 1-[5-cyclopropyl-1-(1-methanesulfonylaminocarbonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 55, the title compound was obtained as a pale-yellow amorphous solid (200 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (500 mg) of Example 2.

Example 57

Production of 1-[5-cyclopropyl-1-(1-methoxycarbonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2 was suspended in chloroform (2.0 ml), and potassium carbonate (177 mg) was added under ice-cooling. Methyl chloroformate (49.4 µl) was added, and the mixture was allowed to return to room temperature and stirred for 1.5 hr. Methyl chloroformate (49.4 µl) was further added, and the mixture was stirred at room temperature for 15.5 hr. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=30:1) to give the title compound as a white amorphous solid (210 mg).

Example 58

Production of 1-{5-cyclopropyl-1-[1-(2-hydroxyethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 57, the title compound was obtained as a white amorphous solid (214 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-

[(S)3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (300 mg) of Example 2.

Example 59

Production of 1-{5-cyclopropyl-1-[1-(2-dimethylaminoethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (166 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (300 mg).

Example 60

Production of 1-{5-cyclopropyl-1-[1-(2-piperidin-1-yl-ethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (219 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (300 mg).

Example 61

Production of 1-{5-cyclopropyl-1-[1-(piperidin-4-yl-oxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 11, the title compound was obtained as a pale-yellow amorphous solid (53 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (102 mg).

Example 62

Production of 1-{5-cyclopropyl-1-[1-(1-methylpiperidin-4-yl-oxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 12, the title

compound was obtained as a white amorphous solid (64 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (124 mg).

Example 63

Production of 1-{1-[1-(1-acetylpiperidin-4-yl-oxycarbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (65 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (122 mg).

Example 64

Production of 1-[1-(1-cyclopropanecarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Chloroform (5 ml) and triethylamine (0.13 ml) were added to 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2 and cyclopropanecarboxylic chloride (0.047 ml) was added under ice-cooling. After stirring overnight at room temperature, the solvent was removed under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:methanol=10:1) to give the title compound as a white amorphous solid (170 mg).

Example 65

Production of 1-{5-cyclopropyl-1-[1-(2-hydroxyacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Chloroform (5 ml) and triethylamine (0.16 ml) were added to 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (250 mg) of Example 2 and acetoxyacetyl chloride (0.069 ml) was added under ice-cooling. After stirring overnight at room temperature, the mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:methanol=10:1). The obtained amorphous solid was dissolved in tetrahydrofuran (2 ml), methanol (2 ml) and water (4 ml), and lithium hydroxide monohydrate (103 mg) was added. The mixture was stirred at 60°C for 4 hrs. The mixture was concentrated under reduced pressure, 5% aqueous potassium hydrogensulfate was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:methanol=20:1) to give the title compound as a white amorphous solid (30 mg).

Example 66

Production of 1-(5-cyclopropyl-1-{1-[1-(4-fluorophenyl)cyclopropanecarbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a pale-yellow amorphous solid (193 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 67

Production of 1-{5-cyclopropyl-1-[1-(2-dimethylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 64, the title compound was obtained as a pale-yellow amorphous solid (217 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 68

Production of 1-{1-[1-(2-acetylaminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a pale-brown yellow amorphous solid (119 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 69

Production of 1-{5-cyclopropyl-1-[1-(1-methylcyclopropanecarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a pale-yellow amorphous solid (178 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 70

Production of 1-{1-[1-(2-acetylamino-2-methylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a pale-brown yellow amorphous solid (94 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 71

Production of 1-(1-{1-[(S)-2-acetylaminopropionyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a white amorphous solid (183 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 72

Production of 1-(1-{1-[(S)-2-acetylamino-3-methylbutyryl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a pale-yellow amorphous solid (212 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 73

Production of 1-{5-cyclopropyl-1-[1-(3,3,3-trifluoropropionyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a pale-yellow amorphous solid (151 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (150 mg) of Example 2.

Example 74

Production of 1-(5-cyclopropyl-1-{1-[(S)-5-oxopyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a white amorphous solid (127 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200

mg) of Example 2.

Example 75

Production of 1-{1-[1-(3-acetylaminopropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a pale-yellow amorphous solid (263 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (355 mg) of Example 2.

Example 76

Production of 1-{5-cyclopropyl-1-[1-(3-hydroxy-2,2-dimethylpropionyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a white amorphous solid (238 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (250 mg) of Example 2.

Example 77

Production of 1-{1-[1-(2-aminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-yellow amorphous solid (219 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 78

1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopropanecarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as while crystals (168 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-

(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (250 mg) of Example 2.

Example 79

Production of 1-{1-[1-(2-amino-2-methylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-brown yellow amorphous solid (154 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 80

Production of 1-{5-cyclopropyl-1-[1-(4-hydroxybutyryl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a white amorphous solid (166 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 81

Production of 1-(5-cyclopropyl-1-{1-[(S)-pyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-yellow amorphous solid (569 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (450 mg).

Example 82

Production of 1-(5-cyclopropyl-1-{1-[(S)-1-methylpyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-yellow amorphous solid (192 mg)

from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (450 mg).

Example 83

Production of 1-{1-[1-(3-aminopropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-yellow amorphous solid (414 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (355 mg) of Example 2.

Example 84

Production of 1-(1-{1-[(S)-2-amino-3-methylbutyryl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-brown yellow amorphous solid (182 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (150 mg) of Example 2.

Example 85

Production of 1-{5-cyclopropyl-1-[1-(2-methylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-brown yellow amorphous solid (183 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (150 mg) of Example 2.

Example 86

Production of 1-{5-cyclopropyl-1-[1-(piperidine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title

compound was obtained as a pale-yellow amorphous solid (478 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (404 mg) of Example 2.

Example 87

Production of 1-{5-cyclopropyl-1-[1-(2-isobutyrylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a pale-brown yellow amorphous solid (214 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 88

Production of 1-{1-[1-(2-cyclopropanecarbonylaminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a pale-yellow amorphous solid (190 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 89

Production of 1-(1-{1-[(S)-1-acetylpyrrolidine-2-carbonyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a pale-yellow amorphous solid (189 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (450 mg).

Example 90

Production of 1-{5-cyclopropyl-1-[1-(2-methanesulfonylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-

carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a white amorphous solid (134 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (152 mg).

Example 91

Production of 1-{1-[1-(1-acetylpiperidine-4-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a pale-yellow amorphous solid (145 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (404 mg) of Example 2.

Example 92

Production of 1-{5-cyclopropyl-1-[1-(1-methylpiperidine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-brown yellow amorphous solid (151 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (404 mg) of Example 2.

Example 93

Production of 1-{1-[1-(3-carbamoylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a white amorphous solid (61 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 94

Production of 1-[1-(1-carbamoylmethylpiperidin-4-yl)-5-

cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2 was dissolved in N,N-dimethylformamide (2.5 ml), and potassium carbonate (93 mg) and 2-bromoacetamide (50.7 mg) were added. The mixture was stirred at room temperature for 2 hr. Water was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give 1-[1-(1-carbamoylmethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (167 mg) as a white amorphous solid.

1-[1-(1-Carbamoylmethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (154 mg)obtained in the previous step was dissolved in ethyl acetate (2 ml), and 4N hydrochloric acid ethyl acetate solution (159 µl) was added. The mixture was stirred for 10 min. The precipitated crystals were collected by filtration and dried to give the title compound as a white amorphous solid (109 mg).

Example 95

Production of 1-[5-cyclopropyl-1-(1-methylcarbamoylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (2.5 g) of Example 2 was dissolved in N,N-dimethylformamide (20 ml), and potassium carbonate (1.62 g) and ethyl bromoacetate (0.98 g) were added. The mixture was stirred at room temperature for 1 hr. Water was added to the reaction mixture, and the mixture was extracted twice with

ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=25:1) to give 1-{5-cyclopropyl-1-[1-(ethoxycarbonylmethyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (2.79 g) as a white amorphous solid.

1-{5-Cyclopropyl-1-[1-(ethoxycarbonylmethyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (1.4 g) obtained in the previous step was dissolved in tetrahydrofuran (5.5 ml) and methanol (2.7 ml), and 4N aqueous sodium hydroxide solution (1.4 ml) was added. The mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was dissolved in water. The aqueous layer was washed twice with diethyl ether, adjusted to pH 5-6 with 2N hydrochloric acid under ice-cooling, and extracted 3 times with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and n-hexane was added to the obtained residue. The precipitated solid was collected by filtration, and dried to give 1-[1-(1-carboxymethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (1.17 g) as a white solid.

N,N-Dimethylformamide (3.0 ml) was added to 1-[1-(1-carboxymethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (150 mg) obtained in the previous step, 1-hydroxybenzotriazole (61 mg), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (76 mg) was added, and the mixture was stirred at room temperature for 1 hr. 40% Aqueous methylamine solution (106 µl) was added, and the mixture was stirred for 5 hr, 40% methylamine aqueous solution (318 µl) was further added, and the mixture was stirred at room temperature for 13 hr. Water

was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution, water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1). The obtained amorphous solid was dissolved in ethyl acetate (2.0 ml), 4N hydrochloric acid ethyl acetate solution (100 µl) was added, and the mixture was stirred for 10 min. The precipitated crystals were collected by filtration and dried to give the title compound as a white amorphous solid (16.9 mg).

Example 96

Production of 1-{1-[1-(1-carbamoyl-1-methylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

Cumylamine (1.1 g) and triethylamine (1.2 ml) were dissolved in chloroform (10 ml), and a solution of 2-bromoisobutyryl bromide (1.0 ml) in chloroform (2 ml) was added under ice-cooling over 5 min. The mixture was stirred at room temperature for 15 min. The mixture was concentrated under reduced pressure, ethyl acetate was added to the obtained residue, and the mixture was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained white solid was washed with diisopropyl ether, and dried to give 2-bromo-2-methyl-N-(1-methyl-1-phenylethyl)-propylamide as a white solid (1.73 g).

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 was dissolved in tetrahydrofuran (5.5 ml), and 60% sodium hydride (104 mg) was added. The mixture was stirred at 60°C for 1 hr and at room temperature for 5 min. 2-Bromo-2-methyl-N-(1-methyl-1-phenylethyl)-propylamide (329 mg) produced in the previous step was added, and the mixture was stirred at 60°C for 22 hr. After allowing to cool, water was added to the reaction mixture, and the

mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give 1-(5-cyclopropyl-1-{1-[1-methyl-1-(1-methyl-1-phenylethylcarbamoyl)ethyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine as a pale-yellow amorphous form (78 mg).

1-(5-Cyclopropyl-1-{1-[1-methyl-1-(1-methyl-1-phenylethylcarbamoyl)ethyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine produced in the previous step was dissolved in trifluoroacetic acid (2 ml), and the mixture was stirred at 80°C for 8 hr. Trifluoroacetic acid (1 ml) was further added and the mixture was further stirred at 80°C for 8 hr. After allowing to cool, and the mixture was concentrated under reduced pressure, and the obtained residue was dissolved in ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:acetone=4:5→chloroform:methanol=10:1). The obtained residue was dissolved in ethyl acetate (1 ml), and 4N hydrochloric acid ethyl acetate solution (1 ml) and diethyl ether (1.5 ml) were added. The obtained solid was collected by filtration and dried to give the title compound as a pale-yellow solid (36 mg).

Example 97

Production of 1-{1-[1-(2-carbamoylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 94, the title compound was obtained as a white amorphous solid (149 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-

[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 98

Production of 1-[5-cyclopropyl-1-(1-cyclopropylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 94, the title compound was obtained as while crystals (133 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (150 mg) of Example 2.

Example 99

Production of 1-[5-cyclopropyl-1-(1-cyclopropylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 94, the title compound was obtained as a pale-brown yellow amorphous solid (144 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 100

Production of 1-[5-cyclopropyl-1-(1-dimethylcarbamoylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 95, the title compound was obtained as a white amorphous solid (20 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (2.5 g) of Example 2.

Example 101

Production of 1-[1-(1-carboxymethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

The title compound was obtained as a white amorphous solid (24 mg) from 1-[1-(1-carboxymethylpiperidin-4-yl)-5-

cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (112 mg) produced in Example 95.

Example 102

Production of 1-[1-(1-carboxyethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 95, the title compound was obtained as a pale-yellow amorphous solid (295 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (350 mg).

Example 103

Production of 1-{1-[1-(1-carbamoylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 95, the title compound was obtained as a pale-yellow amorphous solid (146 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (350 mg).

Example 104

Production of 1-{1-[1-(2-carboxy-2-methylpropyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 95, the title compound was obtained as a pale-yellow amorphous solid (71 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (400 mg).

Example 105

Production of 1-{1-[1-(2-carbamoyl-2-methylpropyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 95, the title

compound was obtained as a white amorphous solid (52 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (400 mg).

Example 106

Production of 1-{1-[1-(1-carbamoylcyclopropylmethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 95, the title compound was obtained as a white amorphous solid (82 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (400 mg).

Example 107

Production of 1-(5-cyclopropyl-1-{1-[1-(2-hydroxyethylcarbamoyl)cyclopropylmethyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 95, the title compound was obtained as a white amorphous solid (84 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (400 mg).

Example 108

Production of 1-[5-cyclopropyl-1-(1-trifluoromethanesulfonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2 was dissolved in methylene chloride (2.0 ml), and under an argon atmosphere, the solution was cooled to -78°C, triethylamine (178 µl) and trifluoromethanesulfonic acid anhydride (78.8 µl) were added, and the mixture was stirred for 2.5 hr.

Trifluoromethanesulfonic acid anhydride (78.8 µl) was further

added and the mixture was stirred for 2 hr. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture at -78°C, and the mixture was extracted with chloroform. The organic layer was washed with 1N hydrochloric acid, water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give the title compound as a yellow amorphous form (192 mg).

Example 109

Production of 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethanesulfonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 108, the title compound was obtained as a yellow amorphous solid (29 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 110

Production of 1-{1-[1-(1-cyanoiminoethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (300 mg) was dissolved in chloroform (5 ml), and triethylamine (97 µl) and methyl N-cyanoacetoimidate (66 µl) were added. After stirring at room temperature for 30 min and at 45°C for 1.5 hr, triethylamine (97 µl) and methyl N-cyanoacetoimidate (66 µl) were further added, and the mixture was stirred at 45°C for 2 hr. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=15:1) to give the title compound as a pale-yellow amorphous form (214 mg).

Example 111

Production of 1-(1-{1-[cyanoimino(methylamino)methyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of 1-(1-{1-[cyanoimino(phenoxy)-methyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Chloroform (5 ml) was added to 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (500 mg) and triethylamine (0.162 ml) and diphenyl N-cyanocarbonimidate (284 mg) were added. The mixture was stirred for 1.5 hr. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:acetone=1:1→2:3→1:2) to give the title compound as a pale-yellow amorphous form (575 mg).

Step 2

Production of 1-(1-{1-[cyanoimino(methylamino)methyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-(1-{1-[Cyanoimino(phenoxy)-methyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (575 mg) produced in the previous step was dissolved in chloroform (10 ml), methylamine hydrochloride (81 mg) and triethylamine (0.31 ml) were added, and the mixture was stirred at room temperature for 30 min and at 55°C for 5 hr. Methylamine hydrochloride (81 mg) and triethylamine (2 ml) further added and the mixture was stirred at 55°C for 1 hr and at 60°C for 30 min. Methylamine hydrochloride (162 mg) was further added and the mixture was stirred at 60°C for 2.5 hr. After allowing to cool, the mixture was concentrated under reduced pressure, and the obtained residue was dissolved in chloroform, and the mixture was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained

residue was purified by silica gel chromatography (chloroform:methanol=10:1) to give the title compound as a white amorphous solid (242 mg).

Example 112

Production of 1-{1-[1-(N-cyanocarbamimidoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 111, the title compound was obtained as a pale-yellow amorphous solid (249 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (302 mg).

Example 113

Production of 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid

Step 1

Production of tert-butyl 1-[1-(4-ethoxycarbonylphenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carboxylate

tert-Butyl 2-cyclopropylcarbonyl-3-dimethylaminoacrylate (1.12 g) produced by a method similar to that of Example 1, Step 1 and ethyl 4-(4-hydrazinopiperidin-1-yl)benzoate hydrochloride (692 mg) produced by a known method were suspended in ethanol (15 ml). Triethylamine (0.81 ml) was added to the obtained suspension, and the mixture was refluxed overnight. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=3:1) to give the title compound as a yellow oil (673 mg).

Step 2

Production of 1-[1-(4-ethoxycarbonylphenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

tert-Butyl 1-[1-(4-ethoxycarbonylphenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carboxylate (673 mg) produced in the previous step was dissolved in chloroform (4 ml), trifluoroacetic acid (4 ml) was added under ice-cooling, and the mixture was stirred at 40°C for 2 hr. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. To the obtained residue were added diethyl ether and n-hexane, and the precipitated solid was collected by filtration and dried to give the title compound as a white solid (556 mg).

Step 3

Production of 5-cyclopropyl-1-{1-[1-(4-ethoxycarbonylphenyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{3-(2-trifluoromethylphenyl)}pyrrolidine

5-Cyclopropyl-1-[1-(4-ethoxycarbonylphenyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid (550 mg) produced in the previous step, 1-hydroxybenzotriazole (285 mg) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (357 mg) were dissolved in N,N-dimethylformamide (8 ml). 3-(2-Trifluoromethylphenyl)pyrrolidine (308 mg) was added to the obtained solution and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (ethyl acetate) to give the title compound as a white amorphous solid (757 mg).

Step 4

Production of 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid

1-{1-[1-(4-Ethoxycarbonylphenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-{3-(2-trifluoromethylphenyl)}pyrrolidine (720 mg) produced in the previous step was dissolved in tetrahydrofuran (3 ml) and methanol (1.5 ml), and 4N aqueous sodium hydroxide solution (1.2 ml) was added. The mixture was stirred at room temperature for 4 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was dissolved in water. The aqueous layer was washed with diethyl ether, acidified with 2N hydrochloric acid under ice-cooling, and extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Diethyl ether:n-hexane (1:1) was added to the obtained residue and the precipitated solid was collected by filtration and dried to give the title compound as a white solid (600 mg).

Example 114

Production of 3-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine (195 mg) produced by a method similar to that of Example 1 and ethyl 3-iodobenzoate (142 mg) were dissolved in 1,4-dioxane (1 ml) and tert-butanol (1 ml), and tris(dibenzylideneacetone)dipalladium (14.2 mg), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (24.3 mg) and cesium carbonate (235 mg) were added. The mixture was heated under reflux overnight. After allowing to cool, the insoluble material was filtered through celite, and the filtrate was concentrated under reduced pressure. A saturated aqueous sodium hydrogen carbonate solution was added to the obtained residue, and the mixture was

extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:acetone=1:1) to give ethyl 3-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoate as a white amorphous solid (179 mg).

Ethyl 3-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoate (179 mg) produced in the previous step was dissolved in tetrahydrofuran (1 ml) and ethanol (1 ml), and 4N aqueous sodium hydroxide solution (1 ml) was added. The mixture was heated under reflux for 2 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was dissolved in water, and acidified with 2N hydrochloric acid under ice-cooling. The precipitated solid was collected by filtration, washed with water and dried under reduced pressure to give the title compound as a white solid (165 mg).

Example 115

Production of 5-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiophene-2-carboxylic acid

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine (220 mg) produced by a method similar to that of Example 1 and ethyl 5-bromothiophene-2-carboxylate (137 mg) were dissolved in toluene (4 ml), and palladium acetate (13 mg), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (36 mg) and cesium carbonate (265 mg) were added. The mixture was heated under reflux for 6 hr. After allowing to cool, the insoluble material was filtered through celite, and the filtrate was concentrated under reduced pressure. A saturated aqueous sodium hydrogen carbonate solution was added to the obtained residue, and the mixture was extracted with ethyl acetate. The

ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:acetone=1:1) to give ethyl 5-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiophene-2-carboxylate (162 mg) as a white amorphous solid.

Ethyl 5-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiophene-2-carboxylate (162 mg) produced in the previous step was dissolved in tetrahydrofuran (1 ml) and ethanol (1 ml), and a 4N aqueous sodium hydroxide solution (1 ml) was added. The mixture was heated under reflux for 3 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was dissolved in water, and acidified with 2N hydrochloric acid under ice-cooling. The precipitated solid was collected by filtration, washed with water and dried under reduced pressure. The obtained solid was purified by silica gel chromatography (chloroform:acetone=6:1), and recrystallized from ethyl acetate to give the title compound as a pale-green solid (28 mg).

Example 116

Production of 2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiazole-4-carboxylic acid

Step 1

Production of 4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidine-1-thiocarboxamide

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine (420 mg) produced by a method similar to that of Example 1 was dissolved in chloroform (10 ml), and triethylamine (0.139 ml) and 9-fluorenylmethoxycarbonylisothiocyanate (285 mg) were added at room temperature. The mixture was stirred for 1 hr. The

reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=50:1). The obtained purified product was dissolved in N,N-dimethylformamide (7 ml), and piperidine (0.7 ml) was added at room temperature. The mixture was stirred for 1 hr and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and the mixture was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Diethyl ether was added to the obtained residue, and the precipitated solid was collected by filtration, washed with water and dried under reduced pressure to give the title compound as a white solid (287 mg).

Step 2

Production of 2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiazole-4-carboxylic acid

4-{5-Cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidine-1-thiocarboxamide (280 mg) produced in the previous step was suspended in ethanol (5 ml), and ethyl bromopyruvate (0.09 ml) was added to the obtained suspension. The mixture was refluxed for 2 hr. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with chloroform. The chloroform layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give ethyl 2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiazole-4-carboxylate (361 mg) as a white amorphous solid.

Ethyl 2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-

yl}piperidin-1-yl)thiazole-4-carboxylate (355 mg) produced in the previous step was dissolved in tetrahydrofuran (0.6 ml) and methanol (0.3 ml), and 4N aqueous sodium hydroxide solution (0.57 ml) was added at room temperature. The mixture was stirred for 3 hr. The reaction mixture was concentrated under reduced pressure, and a 1N aqueous sodium hydroxide solution was added to the obtained residue, and the mixture was washed with diethyl ether. The aqueous layer was acidified with 2N hydrochloric acid, and the precipitated solid was collected by filtration, washed with water and dried under reduced pressure to give the title compound as a white solid (272 mg).

Example 117

Production of 1-{5-cyclopropyl-1-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

Step 1

Production of methyl 4-{5-cyclopropyl-4-[(S)-3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidine-1-imidothiocarboxylate hydroiodide

4-{5-Cyclopropyl-4-[(S)-3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidine-1-thiocarboxamide (500 mg) produced by a method similar to that of Example 116, Step 1 was dissolved in chloroform (5 ml), and methyl iodide (0.1 ml) was added. The mixture was stirred overnight at room temperature. The mixture was concentrated under reduced pressure, diethyl ether was added to the obtained residue, and the precipitated solid was collected by filtration and dried to give the title compound as a pale-yellow solid (654 mg).

Step 2

Production of 1-{5-cyclopropyl-1-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

Methyl 4-{5-cyclopropyl-4-[(S)-3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-

yl}piperidine-1-imidothiocarboxylate hydroiodide (317 mg) produced in the previous step, acetic acid hydrazide (50 mg) and sodium acetate (43 mg) were suspended in dioxane (2 ml) and water (0.4 ml), and the mixture was heated under reflux overnight. The solvent was removed under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=10:1). The obtained amorphous solid was dissolved in ethyl acetate (1 ml), and a 4N hydrochloric acid ethyl acetate solution (0.4 ml) was added. The precipitated solid was collected by filtration and dried to give the title compound as white crystals (72 mg).

Example 118

Production of 1-{5-cyclopropyl-1-[1-(5-cyclopropyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 117, the title compound was obtained as while crystals (253 mg) from methyl 4-{5-cyclopropyl-4-[(S)-3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidine-1-imidothiocarboxylate hydroiodide (475 mg).

Example 119

Production of 1-{5-cyclopropyl-1-[1-(5-hydroxymethyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 117, the title compound was obtained as while crystals (25 mg) from methyl 4-{5-cyclopropyl-4-[(S)-3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidine-1-imidothiocarboxylate hydroiodide (317 mg).

Example 120

Production of 1-{5-cyclopropyl-1-[1-(5-trifluoromethyl-4H-

[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 117, the title compound was obtained as while crystals (130 mg) from methyl 4-{5-cyclopropyl-4-[(S)-3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidine-1-imidothiocarboxylate hydroiodide (317 mg).

Example 121

Production of 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of methyl 5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carboxylate

Methyl 1-(1-benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carboxylate (15.9 g) produced in Example 1, Step 2 was dissolved in methanol (12 ml), and palladium carbon (1.5 g) was added. The mixture was stirred overnight under a hydrogen atmosphere. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. n-Hexane was added to the obtained residue, and filtration gave the title compound as a white amorphous solid (9.66 g).

Step 2

Production of methyl 5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylate

Methyl 5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carboxylate (2.82 g) produced in the previous step was dissolved in chloroform (28 ml) and triethylamine (1.58 ml) was added.

2-Fluorophenylisocyanate (1.4 ml) was added to the obtained mixture under ice-cooling and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=2:3) to

give the title compound as a white amorphous solid (4.23 g).

Step 3

Production of 5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid

Methyl 5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylate (4.23 g) produced in the previous step was dissolved in tetrahydrofuran (11 ml) and methanol (5 ml), and a 4N aqueous sodium hydroxide solution (11 ml) was added. The mixture was stirred at 60°C for 6 hr. The reaction mixture was allowed to cool and concentrated under reduced pressure. The obtained residue was dissolved in water. The aqueous layer was washed with diethyl ether, and acidified with concentrated hydrochloric acid under ice-cooling. The precipitated solid was collected by filtration, washed with water and n-hexane and dried under reduced pressure to give the title compound as a white solid (3.89 g).

Step 4

Production of 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{(R)-3-(2-trifluoromethylphenyl)}pyrrolidine

5-Cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid (101 mg) produced in the previous step, 1-hydroxybenzotriazole (46 mg) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (57 mg) were dissolved in N,N-dimethylformamide (15 ml). (R)-3-(2-Trifluoromethylphenyl)pyrrolidine (65 mg)* and 4-dimethylaminopyridine (37 mg) were added to the obtained solution and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained

residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give the title compound as a white amorphous solid (136 mg).

$[\alpha]^{25}D$=+10.9 (c=0.495, EtOH)

*(R)-3-(2-Trifluoromethylphenyl)pyrrolidine was produced by a method similar to the method of Example 2, Step 1 to Step 4 and using (R)-4-isopropyl-5,5-diphenyloxazolidin-2-one. $[\alpha]^{25}D$=-21.0 (c=0.500, EtOH)

Example 122

Production of 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of methyl 5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylate

1-Methylcyclopropane-1-carboxylic acid (1.81 g), diphenylphosphoryl azide (4.67 ml) and triethylamine (2.77 ml) were dissolved in toluene (30 ml), and the mixture was heated under reflux for 1 hr to produce isocyanate.

Methyl 5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carboxylate (1.50 g) produced in Example 121, Step 1 and triethylamine (0.84 ml) were dissolved in tetrahydrofuran (15 ml) and the toluene solution of isocyanate prepared in advance was added until the starting material, (methyl 1-(piperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carboxylate), disappeared. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with chloroform. The chloroform layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, and dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel chromatography (chloroform:methanol=15:1) to give the title compound as a white amorphous solid (1.92 g).

Step 2

Production of 5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid

Methyl 5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylate (1.92 g) produced in the previous step was dissolved in tetrahydrofuran (20 ml) and methanol (10 ml), and 4N aqueous sodium hydroxide solution (15 ml) was added. The mixture was stirred at 60°C for 6 hr. The reaction mixture was allowed to cool and concentrated under reduced pressure. The obtained residue was dissolved in water and the aqueous layer was washed with diethyl ether. Under ice-cooling, and the mixture was acidified with concentrated hydrochloric acid and extracted with chloroform. The chloroform layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Ethyl acetate was added to the obtained residue, and the precipitated solid was collected by filtration and dried to give the title compound as a white solid (1.68 g).

Step 3

Production of 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine

5-Cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid (91 mg) produced in the previous step, 1-hydroxybenzotriazole (46 mg) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (57 mg) were dissolved in N,N-dimethylformamide (1.5 ml). (R)-3-(2-Trifluoromethylphenyl)pyrrolidine (65 mg) and 4-dimethylaminopyridine (37 mg) were added to the obtained solution and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen

carbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=15:1) to give the title compound as a white amorphous solid (123 mg).

$[\alpha]^{25}D$=+13.1 (c=0.495, EtOH)

Example 123

Production of 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of methyl 5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylate

Methyl 5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carboxylate (1.87 g) produced in Example 121, Step 1 was dissolved in chloroform (20 ml), and triethylamine (1.05 ml) was added. Isopropylisocyanate (0.7 ml) was added to the obtained mixture under ice-cooling and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=15:1) to give the title compound as a white amorphous solid (2.00 g).

Step 2

Production of 5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid

Methyl 5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylate (2.00 g) produced in the previous step was dissolved in tetrahydrofuran (6 ml) and methanol (3 ml), and 4N aqueous sodium hydroxide solution (6 ml) was added. The mixture was stirred at 60°C for 4.5 hr. The reaction mixture was allowed to cool and concentrated under reduced pressure. The obtained residue was dissolved in water and the aqueous layer was washed

with diethyl ether, and acidified with concentrated hydrochloric acid under ice-cooling. The mixture was extracted with chloroform. The chloroform layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure.

n-Hexane was added to the obtained residue, and the precipitated solid was collected by filtration and dried to give the title compound as a white solid (1.58 g).

Step 3

Production of 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine

5-Cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid (88 mg) produced in the previous step, 1-hydroxybenzotriazole (46 mg) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (57 mg) were dissolved in N,N-dimethylformamide (1.5 ml). (R)-3-(2-Trifluoromethylphenyl)pyrrolidine (65 mg) and 4-dimethylaminopyridine (37 mg) was added to the obtained solution and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=15:1) to give the title compound as a white amorphous solid (120 mg).

$[\alpha]^{25}D$=+14.2 (c=0.500, EtOH)

Example 124

Production of 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 121, Step 4, the title compound was obtained as a white amorphous solid (127 mg)

from 5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid (123 mg), (S)-3-(2-trifluoromethylphenyl)pyrrolidine (78 mg).

$[\alpha]^{25}D$=-10.8 (c=0.510, EtOH)

Example 125

Production of 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 123, Step 3, the title compound was obtained as a white amorphous solid (123 mg) from 5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid (107 mg), (S)-3-(2-trifluoromethylphenyl)pyrrolidine (79 mg).

$[\alpha]^{25}D$=-13.2 (c=0.515, EtOH)

Example 126

Production of 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 122, Step 3, the title compound was obtained as a white amorphous solid (149 mg) from 5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid (107 mg), (S)-3-(2-trifluoromethylphenyl)pyrrolidine (76 mg).

$[\alpha]^{25}D$=-13.6 (c=0.500, EtOH)

Example 127

Production of (-)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride

Step 1

Production of ethyl cyano-(4-fluorophenyl)acetate

Toluene (40 ml) was added to 4-fluorophenylacetonitrile (15.0 g) and diethyl carbonate (66.9 ml) and sodium ethoxide (8.30 g) were added. The mixture was stirred for 2 hr while evaporating the solvent at 110°C to 130°C. After allowing to

cool, the reaction mixture was poured into water, and acetic acid (13 ml) was added. The mixture was stirred for 5 min, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound as a pale-yellow oil (25.0 g).

Step 2

Production of diethyl 2-cyano-2-(4-fluorophenyl)succinate

Tetrahydrofuran (40 ml) was added to 60% sodium hydride (2.12 g), and a solution of ethyl cyano-(4-fluorophenyl) acetate (10.0 g) produced in the previous step in tetrahydrofuran (40 ml) was added dropwise under ice-cooling. The mixture was stirred for 40 min and ethyl bromoacetate (6.4 ml) was added under ice-cooling. The mixture was stirred at room temperature for 3 hrs. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=5:1) to give the title compound as a pale-yellow oil (14.7 g).

Step 3

Production of ethyl 3-(4-fluorophenyl)-5-oxo-pyrrolidine-3-carboxylate

A solution of diethyl 2-cyano-2-(4-fluorophenyl)succinate (7.0 g) produced in the previous step in ethanol (50 ml) was added to Raney nickel (7.0 g), and the mixture was stirred overnight under a hydrogen atmosphere. The reaction mixture was filtered through celite, and the filtrate and washing were combined and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=25:1) and a mixed solvent of diethyl ether and n-hexane was added to the obtained solid residue. The

mixture was filtered and dried to give the title compound as white crystals (3.96 g).

Step 4

Production of ethyl 1-benzyl-3-(4-fluorophenyl)-5-oxo-pyrrolidine-3-carboxylate

Tetrahydrofuran (25 ml) was added to 60% sodium hydride (1.63 g), and a solution of ethyl 3-(4-fluorophenyl)-5-oxo-pyrrolidine-3-carboxylate (10.3 g) produced in the previous step in tetrahydrofuran (30 ml)/N,N-dimethylformamide (10 ml) was added dropwise under ice-cooling. The mixture was stirred for 10 min. Under ice-cooling, benzyl bromide (4.86 ml) was added. The mixture was stirred at the same temperature for 30 min and at room temperature for 3.5 hr. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=2:1) to give the title compound as a pale-yellow oil (12.1 g).

Step 5

Production of 1-benzyl-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine

Tetrahydrofuran (20 ml) was added to aluminum lithium hydride (1.16 g) and a solution of ethyl 1-benzyl-3-(4-fluorophenyl)-5-oxo-pyrrolidine-3-carboxylate (4.16 g) produced in the previous step in tetrahydrofuran (20 ml) was added dropwise under ice-cooling. The mixture was stirred under reflux for 3.5 hr. After allowing to cool, water (0.9 ml), 4N aqueous sodium hydroxide solution (0.9 ml) and water (2.7 ml) were successively added under ice-cooling, and diethyl ether and magnesium sulfate were added. The mixture was stirred for 20 min and filtered through celite. The filtrate and washing were combined and concentrated under reduced pressure to give the title compound as a pale-yellow oil (3.18 g).

Step 6

Production of 3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine

To a solution of 1-benzyl-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine (3.18 g) produced in the previous step in methanol (30 ml) was added palladium hydroxide (300 mg), and the mixture was stirred overnight under a hydrogen atmosphere (3 atm). The reaction mixture filtered through celite, and the filtrate and washing were combined and concentrated under reduced pressure to give the title compound as a pale-yellow oil (2.30 g).

Step 7

Production of tert-butyl 3-(4-fluorophenyl)-3-hydroxymethyl-pyrrolidine-1-carboxylate

To 3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine (2.30 g) produced in the previous step were added tetrahydrofuran (40 ml) and triethylamine (5.7 ml), and di-tert-butyldicarbonate (4.60 g) was added under ice-cooling. The mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and ethyl acetate was added. The mixture was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=2:1) to give the title compound as a colorless oil (2.70 g).

Step 8

Production of (-)-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine

To tert-butyl 3-(4-fluorophenyl)-3-hydroxymethyl-pyrrolidine-1-carboxylate (1.02 g) produced in the previous step were added chloroform (10 ml), triethylamine (962 µl) and 4-dimethylaminopyridine (421 mg), and (S)-(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride (969 µl) was added under ice-cooling. The mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the mixture was extracted 3 times with ethyl acetate. The organic layer was

washed with aqueous potassium hydrogensulfate solution, water, aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:diethyl ether=5:3) to give less polar diastereomer as a colorless oil (871 mg). In addition, a more polar diastereomer was obtained as a colorless oil (781 mg).

The colorless oil (871 mg) of the less polar diastereomer was dissolved in tetrahydrofuran (4 ml) and methanol (2 ml), and 4N aqueous sodium hydroxide solution (2.6 ml) was added. The mixture was stirred at 60°C for 40 min. The reaction mixture was concentrated under reduced pressure and water was added to the residue. The mixture was extracted 3 times with diethyl ether. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a colorless oil (481 mg).

Methanol (3 ml) and a 4N hydrochloric acid ethyl acetate solution (3.3 ml) were added to the obtained colorless oil (481 mg) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and water was added to the residue. The mixture was washed with diethyl ether, and the aqueous layer was alkalified with a 2N aqueous sodium hydroxide solution. The mixture was extracted 5 times with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure to give the title compound as a colorless oil (312 mg).

$[\alpha]^{25}D$=-9.70 (c=0.598, EtOH)

Production of (+)-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine

By a method similar to the method for the production of (-)-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine and using a colorless oil (781 mg) of a more polar diastereomer, the title compound was obtained as a colorless oil (251 mg).

$[\alpha]^{25}D$=+10.37 (c=0.588, EtOH)

Step 9

Production of tert-butyl 5-(1-methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carboxylate

tert-Butyl 5-(1-methylcyclopropyl)-1-(piperidin-4-yl)-1H-pyrazole-4-carboxylate (1.15 g) produced by a method similar to that of Example 121, Step 1 and 2-chloropyrimidine (700 mg) were dissolved in 1,4-dioxane (12 ml), and palladium acetate (85 mg), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (352 mg) and cesium carbonate (1.84 g) were added. The mixture was heated under reflux for 3 hr. After allowing to cool, the insoluble material was filtered through celite, and the filtrate was concentrated under reduced pressure. A saturated aqueous sodium hydrogen carbonate solution was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=2:1) to give the title compound as a white amorphous solid (922 mg).

Step 10

Production of 5-(1-methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carboxylic acid hydrochloride

tert-Butyl 5-(1-methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carboxylate (922 mg) produced in the previous step was dissolved in chloroform (2 ml), and trifluoroacetic acid (4 ml) was added. The mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and the obtained crystal was dissolved in tetrahydrofuran. A 4N hydrochloric acid ethyl acetate solution (2 ml) was added, and the mixture was concentrated under reduced pressure. The obtained crystalline residue was slurry washed with ethyl acetate (10 ml) for 1 hr to give the title compound as a white solid (800 mg).

Step 11

Production of (-)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-

pyrazole-4-carbonyl}pyrrolidine hydrochloride

5-(1-Methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carboxylic acid hydrochloride (150 mg) produced in the previous step, 1-hydroxybenzotriazole (81 mg) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (102 mg) were dissolved in N,N-dimethylformamide (3 ml).

(-)-3-(4-Fluorophenyl)-3-hydroxymethylpyrrolidine (88 mg) produced in Step 8, triethylamine (0.057 ml) and 4-dimethylaminopyridine (50 mg) were added to the obtained solution, and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (chloroform:methanol=20:1) and the obtained free base was dissolved in methanol (3 ml). A 4N hydrochloric acid 1,4-dioxane solution (0.2 ml) was added, and the mixture was concentrated under reduced pressure. The obtained crystalline residue was washed in the slurry with ethyl acetate (3 ml) for 15 min to give the title compound as white crystals (203 mg).

$[\alpha]^{25}D$=-21.3 (c=0.506, MeOH)

Example 128

Production of (+)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride

By a method similar to that of Example 127, Step 11, the title compound was obtained as white crystals (198 mg) from 5-(1-methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carboxylic acid hydrochloride (150 mg), (+)-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine (88 mg) produced in Example 127, Step 8.

$[\alpha]^{25}D$=+26.0 (c=0.508, MeOH)

Example 129

Production of 1-[5-cyclopropyl-1-(1-pyrazin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

The title compound was obtained as a yellow amorphous solid (165 mg) from 1-[5-cyclopropyl-1-(1-pyrazin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carboxylic acid hydrochloride (281 mg) produced by a method similar to that of Example 127.

Example 130

Production of 1-[1-(trans-4-carbamoylcyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of ethyl trans-4-(2-tert-butoxycarbonylhydrazino)cyclohexanecarboxylate

Ethyl 4-cyclohexanonecarboxylate (8.0 g) and tert-butyl carbazate (6.2 g) were dissolved in chloroform (150 ml), and acetic acid (5.4 ml) and sodium triacetoxyborohydride (30 g) were added under ice-cooling. The mixture was allowed to gradually return to room temperature, and the mixture was stirred for 7 hr. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=4:1) to give the title compound as a white solid (4.63 g).

Step 2

Production of ethyl trans-4-hydrazinocyclohexanecarboxylate hydrochloride

Ethyl trans-4-(2-tert-butoxycarbonylhydrazino)cyclohexanecarboxylate (4.63 g) produced in the previous step was dissolved in ethanol (30 ml), and a 4N hydrochloric acid ethyl acetate solution (82 ml) was

added. The mixture was stirred for 5.5 hr. The mixture was concentrated under reduced pressure, and diethyl ether was added to the obtained residue. The mixture was filtered and dried to give the title compound as a white powder (3.86 g).

Step 3

Production of tert-butyl 1-(trans-4-ethoxycarbonylcyclohexane)-5-cyclopropyl-1H-pyrazole-4-carboxylate

Ethyl trans-4-hydrazinocyclohexanecarboxylate hydrochloride (3.80 g) obtained in the previous step and tert-butyl 2-cyclopropylcarbonyl-3-dimethylaminoacrylate (3.71 g) synthesized by a method similar to that of Example 1, Step 1 were dissolved in ethanol (50 ml), and triethylamine (4.32 ml) was added. The mixture was stirred under reflux for 1 hr. After allowing to cool, the mixture was concentrated under reduced pressure, and water was added to the residue. The mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=5:1) to give the title compound as a yellow liquid (4.80 g).

Step 4

Production of 1-(trans-4-ethoxycarbonylcyclohexane)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

To a solution of tert-butyl 1-(trans-4-ethoxycarbonylcyclohexane)-5-cyclopropyl-1H-pyrazole-4-carboxylate (4.80 g) obtained in the previous step in chloroform (14 ml) was added trifluoroacetic acid (14 ml), and the mixture was heated to 40°C and stirred for 1.5 hr. After allowing to cool, the mixture was concentrated under reduced pressure and azeotroped with toluene. Ethyl acetate was added to the residue to allow crystal precipitation. The mixture was once concentrated under reduced pressure, n-hexane was added to the residue, and the crystals were collected by filtration and dried to give the title compound as a white powder (3.09 g).

Step 5

Production of 1-{5-cyclopropyl-1-(trans-4-ethoxycarbonylcyclohexyl)-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-(trans-4-Ethoxycarbonylcyclohexane)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid (1.50 g) produced in the previous step and (S)-3-(2-trifluoromethylphenyl)pyrrolidine (1.16 g) were dissolved in N,N-dimethylformamide (15 ml), and 1-hydroxybenzotriazole (825 mg), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1.03 g) and 4-dimethylaminopyridine (658 mg) were added. The mixture was stirred at room temperature for 14 hrs. Ethyl acetate was added to the reaction mixture and the mixture was washed twice with water. The organic layer was washed with 1N hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate solution, water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give the title compound as a brown amorphous (2.34 g).

Step 6

Production of 1-[1-(trans-4-carboxycyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-{5-Cyclopropyl-1-(trans-4-ethoxycarbonylcyclohexyl)-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (2.34 g) produced in the previous step was dissolved in tetrahydrofuran (12 ml) and methanol (6 ml), and a solution of lithium hydroxide monohydrate (973 mg) in water (12 ml) was added. The mixture was stirred at 45°C for 1 hr. The mixture was concentrated under reduced pressure, and water was added to the obtained residue. The mixture was washed twice with diethyl ether, and the aqueous layer was acidified with 2N hydrochloric acid and extracted 3 times with ethyl acetate. The organic layer was

washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Ethyl acetate and n-hexane were added to the obtained residue, and the precipitated solid was collected by filtration and dried to give the title compound as a milky white solid (2.13 g).

Step 7

Production of 1-[1-(trans-4-carbamoylcyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[1-(trans-4-Carboxycyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (300 mg) produced in the previous step was dissolved in N,N-dimethylformamide (3.5 ml), and 1-hydroxybenzotriazole (106 mg), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (133 mg), ammonium chloride (80 mg) and triethylamine (0.105 ml) were added. The mixture was stirred at room temperature for 15 hr. Ethyl acetate was added to the reaction mixture, and the mixture was washed successively with water, 1N hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate solution, water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Diethyl ether was added to the obtained solid residue and the mixture was stirred for 10 min. The solid was collected by filtration and dried to give the title compound as a white amorphous solid (171 mg).

Example 131

Production of 1-[5-cyclopropyl-1-(trans-4-ureidocyclohexyl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Toluene (3.0 ml) was added to 1-[1-(trans-4-carboxycyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg) produced in Example 130, Step 6, and triethylamine (76 µl) and diphenylphosphonic azide (118 µl) were added under an argon atmosphere. The mixture was heated under reflux for 2 hr.

After allowing to cool, the toluene solution was added dropwise to a solution of 28% aqueous ammonia (10 ml) and ethyl acetate (4 ml) under ice-cooling, and the mixture was stirred at the same temperature for 30 min. Water was added to the reaction mixture, and the mixture was extracted 3 times with chloroform. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=10:1). Diethyl ether was added to the obtained solid residue and the mixture was stirred for 10 min. The solid was collected by filtration and dried to give the title compound as a white amorphous solid (135 mg).

Example 132

Production of 1-{5-cyclopropyl-1-[trans-4-(1H-tetrazol-5-yl)cyclohexyl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of 1-[1-(trans-4-cyanocyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[1-(trans-4-Carbamoylcyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (514 mg) produced in Example 130, Step 7 was dissolved in tetrahydrofuran (6 ml), and pyridine (180 µl) and trifluoromethanesulfonic acid anhydride (220 µl) were added. The mixture was stirred at room temperature for 1 hr. Pyridine (180 µl) and trifluoromethanesulfonic acid anhydride (220 µl) were further added, and the mixture was stirred at room temperature for 1 hr. The mixture was concentrated under reduced pressure, and 1N aqueous potassium hydrogensulfate solution was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by chromatography

(chloroform:methanol=15:1) to give the title compound as a pale-yellow amorphous form (207 mg).

Step 2

Production of 1-{5-cyclopropyl-1-[trans-4-(1H-tetrazol-5-yl)cyclohexyl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[1-(trans-4-Cyanocyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (207 mg) produced in the previous step was dissolved in 1,4-dioxane (2.5 ml), and azidotributyltin (188 mg) was added. The mixture was heated under reflux overnight. Azidotributyltin (94 mg) was further added and the mixture was heated under reflux for 4 hr. The mixture was concentrated under reduced pressure, 1N hydrochloric acid was added, and the mixture was extracted twice with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by chromatography (chloroform:methanol=25:2) and concentrated under reduced pressure. Diisopropyl ether was added to the obtained residue, and the precipitated solid was collected by filtration, and dried to give the title compound as a white amorphous solid (122 mg).

Example 133

Production of 1-{5-(1-methylcyclopropyl)-1-[1-(4-trifluoromethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 134

Production of 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-methoxycyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 135

Production of 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-phenyl-3-trifluoromethyl-pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 136

Production of 3-(2-chlorophenyl)-1-{5-cyclopropyl-1-[1-(2,4-difluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 137

Production of 3-(2-chloropyridin-3-yl)-1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 138

Production of 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(2,2,3,3-tetramethylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 139

Production of 1-{5-cyclohexyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 140

Production of 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethoxyphenyl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 141

Production of 1-{5-cyclopropyl-1-[1-(4-trifluoromethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 142

Production of 1-(5-cyclopropyl-1-{1-[((S)-1-carboxy-2-methyl-propyl)methylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 12, the title compound was obtained from the corresponding starting compound.

Example 143

Production of 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-methoxy-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 144

Production of 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-hydroxymethylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 145

Production of 1-{5-cyclopropyl-1-[1-(thiazol-2-ylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 10, the title compound was obtained from the corresponding starting compound.

Example 146

Production of 1-{1-[1-(isopropoxycarbamoyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 10, the title

compound was obtained from the corresponding starting compound.

Example 147

Production of 1-{5-cyclopropyl-1-[1-(4-fluorobenzylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 10, the title compound was obtained from the corresponding starting compound.

Example 148

Production of 1-{1-[1-(2,3-dihydroindole-1-carbonyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 10, the title compound was obtained from the corresponding starting compound.

Example 149

Production of 1-{1-[1-(2,3-dihydro[1,4]oxazine-4-carbonyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 10, the title compound was obtained from the corresponding starting compound.

Example 150

Production of 1-{5-cyclopropyl-1-[1-(2,6-dichloropyridin-3-ylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 10, the title compound was obtained from the corresponding starting compound.

Example 151

Production of 1-{5-(1-methylcyclopropyl)-1-[1-(2,3,4,5-tetrahydrobenzo[b]azepine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 10, the title compound was obtained from the corresponding starting compound.

Example 152

Production of ethyl 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoate

By a method similar to that of Example 114, the title compound was obtained from the corresponding starting compound.

Example 153

Production of 1-[1-(1-benzyloxycarbonyl-piperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 1, Step 4, the title compound was obtained.

Example 154

Production of 1-{1-[1-(3-carboxy-3-methyl-butyryl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 65, the title compound was obtained from the corresponding starting compound.

Example 155

Production of 1-{5-cyclopropyl-1-[1-(2-phenoxyacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 64, the title compound was obtained from the corresponding starting compound.

Example 156

Production of 1-{1-[1-(3-chlorobenzoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 64, the title compound was obtained from the corresponding starting compound.

Example 157

Production of 1-{1-[1-(2-chlorobenzoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 64, the title compound was obtained from the corresponding starting compound.

Example 158

Production of 1-[5-cyclopropyl-1-(1-oxalylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 65, the title compound was obtained from the corresponding starting compound.

Example 159

Production of 1-{1-[1-(4-chlorobenzoyl)piperidin-4-yl]-5-

cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 64, the title compound was obtained from the corresponding starting compound.

Example 160

Production of 1-(5-cyclopropyl-1-{1-[2-(4-fluorophenyl)acetyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 64, the title compound was obtained from the corresponding starting compound.

Example 161

Production of 1-{5-cyclopropyl-1-[1-(3-trifluoromethylbenzoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 64, the title compound was obtained from the corresponding starting compound.

Example 162

Production of 1-{5-cyclopropyl-1-[1-(3-methoxybenzoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 64, the title compound was obtained from the corresponding starting compound.

Example 163

Production of 1-{1-[1-(4-fluorobenzyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine hydrochloride

By a method similar to that of Example 94, the title compound was obtained from the corresponding starting compound.

Example 164

Production of 1-[1-(1-benzenesulfonyl-piperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 108, the title compound was obtained from the corresponding starting compound.

Example 165

Production of 1-{1-[1-(4-carbamoylphenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-

trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 166

Production of 1-{5-cyclopropyl-1-[1-(4-hydroxymethylphenyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 167

Production of 1-{1-[1-(5-carbamoyl-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 168

Production of 1-{1-[1-(4-aminophenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 169

Production of 1-(5-cyclopropyl-1-{1-[4-(2-oxooxazolidin-3-yl)phenyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 170

Production of 1-(5-cyclopropyl-1-{1-[4-(3-methoxyureido)phenyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 171

Production of 1-{5-cyclopropyl-1-[1-(4-

methanesulfonylaminophenyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 172

Production of 1-[1-(1-ethoxycarbamoylpiperidin-4-yl)-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 10, the title compound was obtained from the corresponding starting compound.

Example 173

Production of 1-[1-(5-chloropyridin-2-yl)azetidin-3-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 174

Production of 1-{1-[1-(5-chloro-pyridin-2-yl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-methoxymethyl-3-phenylpyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 175

Production of 1-{1-[1-(5-cyano-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 176

Production of 3-(2-acetoxyethyl)-3-(4-fluorophenyl)-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 177

Production of {(3S*,4R*)-3-methyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-4-phenylpyrrolidine hydrochloride

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 178

Production of methyl 6-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)nicotinate

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 179

Production of methyl 2-{1-[5-(1-methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]pyrrolidin-3-yl}benzoate

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 180

Production of 3-(2-hydroxymethylphenyl)-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 181

Production of 1-[5-cyclopropyl-1-(1-pyridin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-hydroxy-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 182

Production of 1-{1-[1-(4-acetylaminophenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 114, the title compound was obtained from the corresponding starting compound.

Example 183

Production of Sodium 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)-3-fluorobenzoate

By a method similar to that of Example 114, the title compound was obtained from the corresponding starting compound.

Example 184

Production of 3-(2-cyanophenyl)-1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine

By a method similar to that of Example 121, the title compound was obtained from the corresponding starting compound.

Example 185

Production of 3-hydroxymethyl-1-{1-[1-(4-methoxypyrimidin-2-yl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-phenylpyrrolidine hydrochloride

By a method similar to that of Example 127, the title compound was obtained from the corresponding starting compound.

Example 186

Production of 3-(3,5-difluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride

By a method similar to that of Example 127, the title compound was obtained from the corresponding starting compound.

Example 187

Production of 1-{1-[1-(3-chloro-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 188

Production of 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(thiazol-2-yl)pyrrolidine

By a method similar to that of Example 121, the title compound was obtained from the corresponding starting compound.

Example 189

Production of (S)-2-[(trans-4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)-pyrrolidine-1-carbonyl]-pyrazol-1-yl}-cyclohexanecarbonyl)-methyl-amino]-3-methylbutyric acid

By a method similar to that of Example 130, the title compound was obtained from the corresponding starting compound.

Example 190

Production of 1-{5-(1-methylcyclopropyl)-1-[trans-4-(2-fluorophenylcarbamoyl)cyclohexyl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 130, the title compound was obtained from the corresponding starting compound.

Example 191

Production of cis-4-{5-(1-methylcyclopropyl)-4-[3-(2-trifluoromethylphenyl)-pyrrolidine-1-carbonyl]-pyrazol-1-yl}-cyclohexanecarboxylic acid

By a method similar to that of Example 130, the title compound was obtained from the corresponding starting compound.

The structural formula and property values of the compound of each Example are shown in the following Table 1-1 to Table 1-45.

Table 1-1

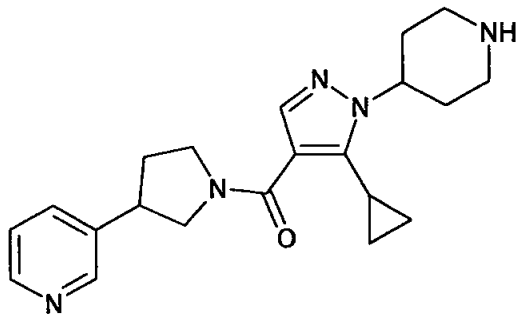
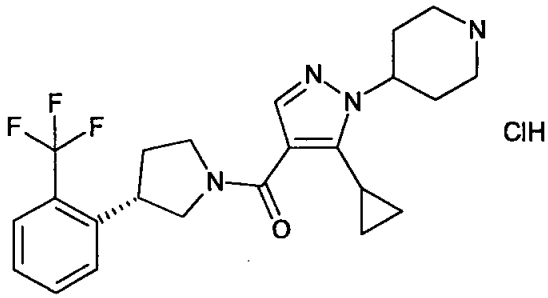
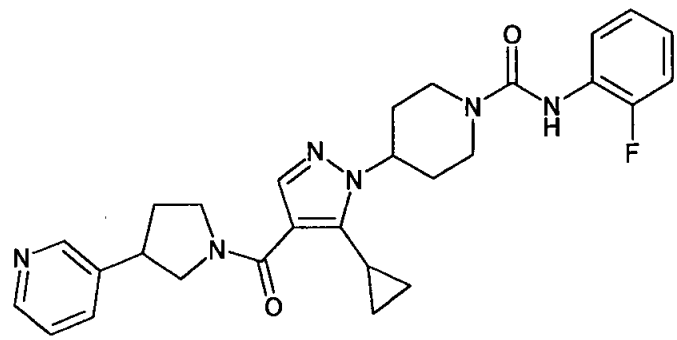
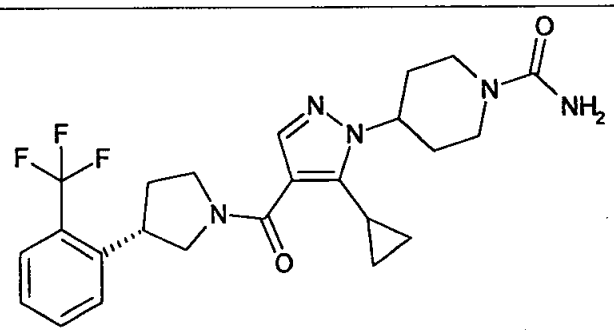
Ex. No.	structural formula	NMR
1		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.63-0.77 (2H, m), 0.97-1.11 (2H, m), 1.70-1.82 (1H, m), 1.96-2.67 (8H, m), 2.83-2.97 (2H, m), 3.33-3.53 (3H, m), 3.55-4.17 (3H, m), 4.50-4.64 (1H, m), 7.23-7.32 (1H, m), 7.48-7.64 (2H, m), 8.46-8.61 (2H, m)
2		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.59-0.75 (2H, m), 0.94-1.07 (2H, m), 1.86-2.36 (8H, m), 3.00-3.21 (2H, m), 3.30-3.93 (6H, m), 4.69-4.88 (1H, m), 7.44-7.64 (2H, m), 7.66-7.78 (3H, m), 8.83 (1H, brs), 9.22 (1H, brs)
3		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.83 (2H, m), 0.99-1.15 (2H, m), 1.73-1.84 (1H, m), 1.90-2.50 (6H, m), 3.02-3.20 (2H, m), 3.36-3.55 (1.5H, m), 3.56-3.80 (2H, m), 3.83-3.99 (1H, m), 4.06-4.17 (0.5H, m), 4.18-4.36 (2H, m), 4.54-4.71 (1H, m), 6.71 (1H, brs), 6.93-7.00 (1H, m), 7.02-7.14 (2H, m), 7.24-7.32 (1H, m), 7.50-7.62 (2H, m), 8.02-8.09 (1H, m), 8.47-8.59 (2H, m)
4		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.84 (2H, m), 1.03-1.14 (2H, m), 1.54-2.47 (7H, m), 2.94-3.14 (2H, m), 3.40-4.20 (7H, m), 4.47-4.67 (2H, m), 7.32-7.72 (6H, m)

Table 1-2

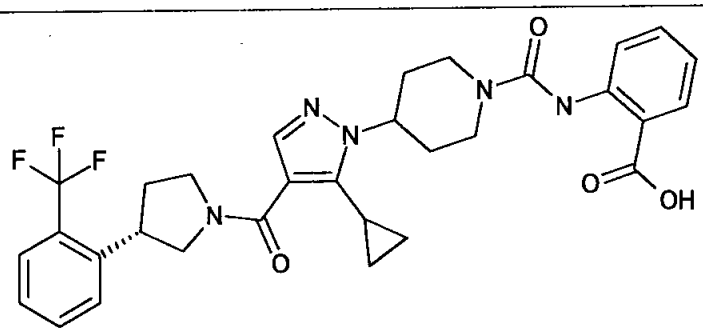
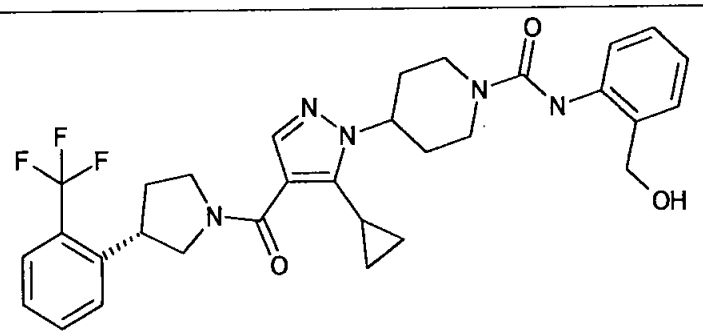
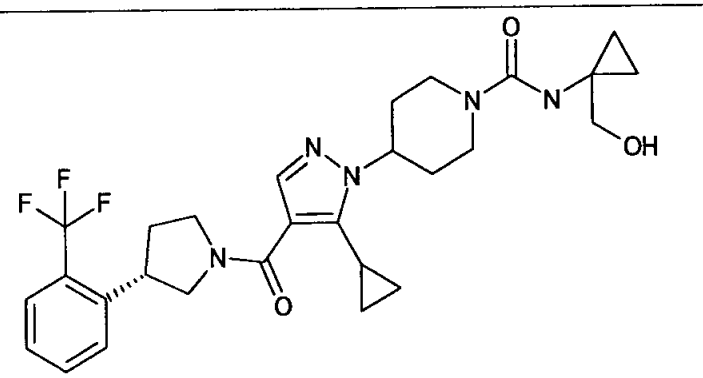
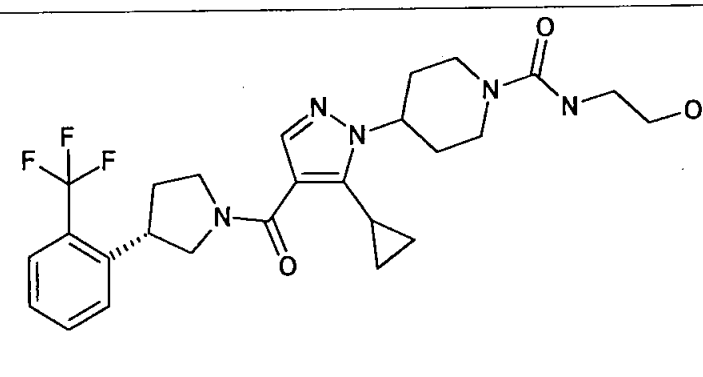
Ex. No.	structural formula	NMR
5		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.75 (2H, m), 0.92-1.07 (2H, m), 1.81-2.36 (6H, m), 3.04-3.23 (2H, m), 3.44-3.93 (6H, m), 4.10-4.27 (2H, m), 4.65-4.83 (1H, m), 6.98-7.07 (1H, m), 7.39-7.61 (3H, m), 7.63-7.79 (3H, m), 7.92-8.02 (1H, m), 8.37-8.40 (1H, m), 11.0-11.2 (1H, m), 13.6 (1H, brs)
6		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.85 (2H, m), 1.01-1.14 (2H, m), 1.70-2.44 (7H, m), 2.72-2.86(1H, m), 2.97-3.13 (2H, m), 3.41-4.09 (5H, m), 4.20-4.35 (2H, m), 4.51-4.75 (3H, m), 6.97-7.04 (1H, m), 7.11-7.19 (1H, m), 7.28-7.60 (5H, m), 7.64-7.72 (1H, m), 7.92-7.98 (1H, m), 8.13-8.23 (1H, m)
7		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.61-0.94 (6H, m), 0.98-1.17 (2H, m), 1.64-1.86 (3H, m), 1.93-2.23 (3H, m), 2.24-2.48 (1H, m), 2.79-2.99 (2H, m), 3.32-4.22 (9H, m), 4.38-4.63 (1H, m), 5.64-5.87 (1H, m), 7.29-7.60 (4H, m), 7.60-7.71 (1H, m)
8		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.66-0.82 (2H,m), 0.99-1.12 (2H, m), 1.20-1.34 (1H, m), 1.67-1.88 (4H, m), 1.95-2.21 (3H,m), 2.23-2.46 (1H, m), 2.82-3.02 (2H, m), 3.28-3.48 (3H, m), 3.52-3.99 (5H, m), 3.99-4.22 (2H, m), 4.41-4.63 (1H, m), 5.16-5.33 (1H, m), 7.28-7.71 (5H, m)

Table 1-3

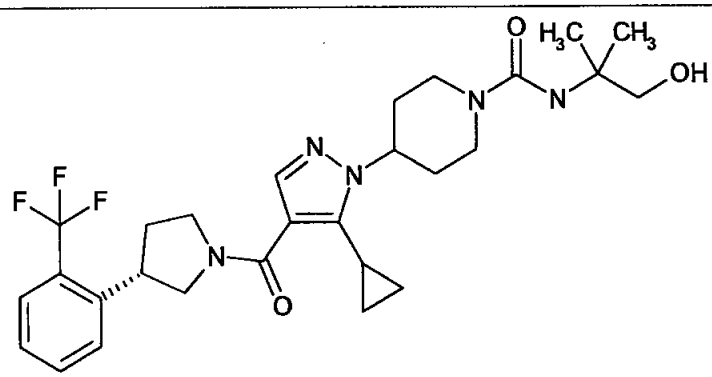
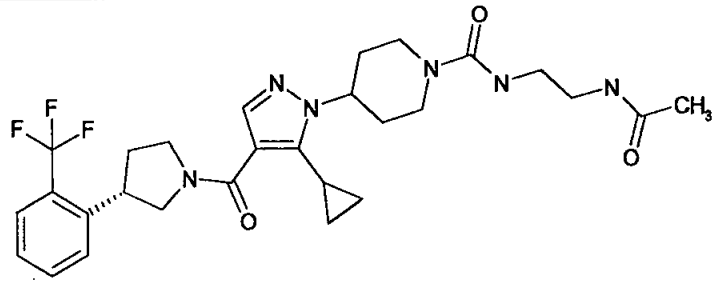
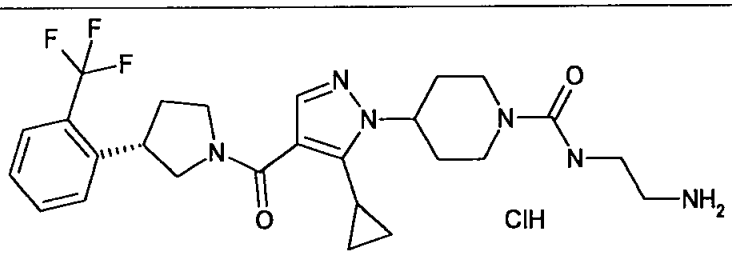
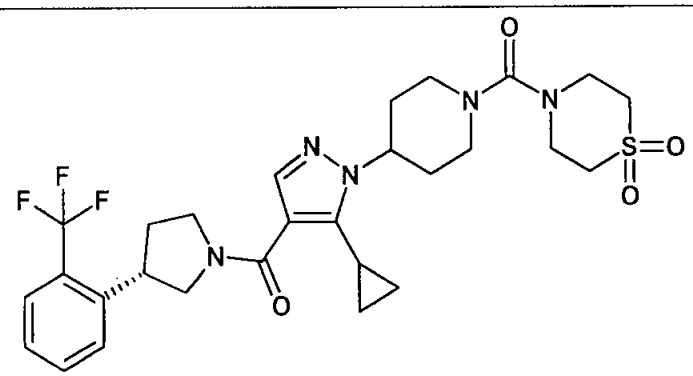
Ex. No.	structural formula	NMR
9		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.87 (2H, m), 0.98-1.17 (2H, m), 1.31 (3H, s), 1.32 (3H, s), 1.66-2.25 (6H, m), 2.26-2.47 (1H, m), 2.83-3.02 (2H, m), 3.39-4.20 (9H, m), 4.43-4.64 (1H, m), 4.67-4.84 (1H, m), 5.00-5.46 (1H, brs), 7.32-7.40 (1H, m), 7.41-7.60 (3H, m), 7.61-7.72 (1H, m)
10		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.82 (2H, m), 1.00-1.11 (2H, m), 1.70-1.83 (1H, m), 1.83-1.95 (3H, m), 1.99 (3H, br s), 2.04-2.22 (3H, m), 2.27-2.43 (1H, m), 2.86-3.01 (2H, m), 3.33-3.43 (4H, m), 3.54-4.18 (6H, m), 4.44-4.63 (1H, m), 5.42-5.53 (1H, m), 6.33-6.41 (1H, m), 7.32-7.71 (5H, m)
11		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.58-0.74 (2H,m), 0.91-1.05 (2H, m), 1.78-2.34 (7H, m), 2.78-2.99 (5H, m), 3.22-3.94 (6H,m), 4.06-4.21 (2H, m), 4.54-4.72 (1H, m), 6.46-6.95 (1H,m), 7.42-7.77 (5H, m), 7.88-8.03 (3H,m)
12		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.86 (2H, m), 1.01-1.16 (2H, m), 1.71-1.86 (1H, m), 1.89-2.46 (6H, m), 2.91-3.15 (6H, m), 3.40-4.14 (11H, m), 4.47-4.67 (1H, m), 7.32-7.73 (5H, m)

Table 1-4

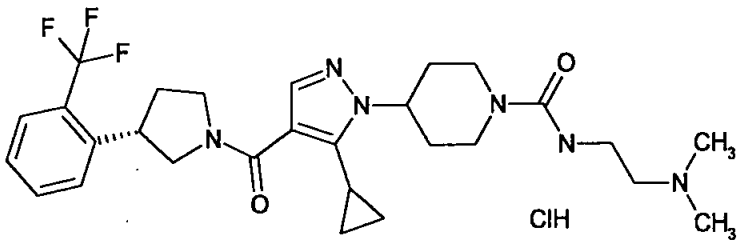
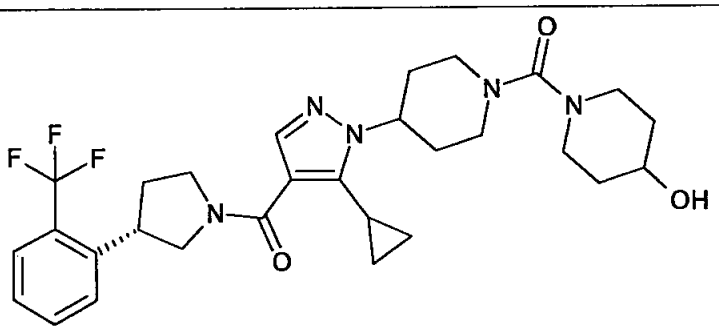
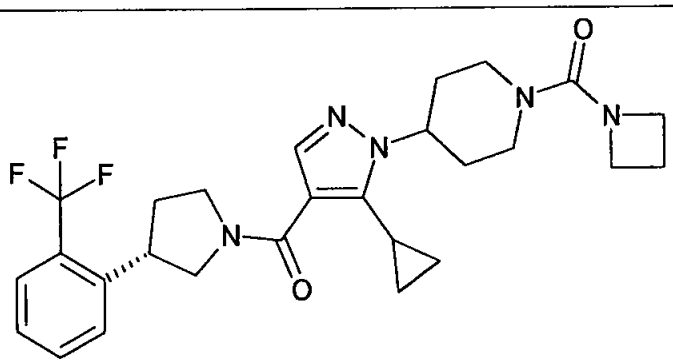
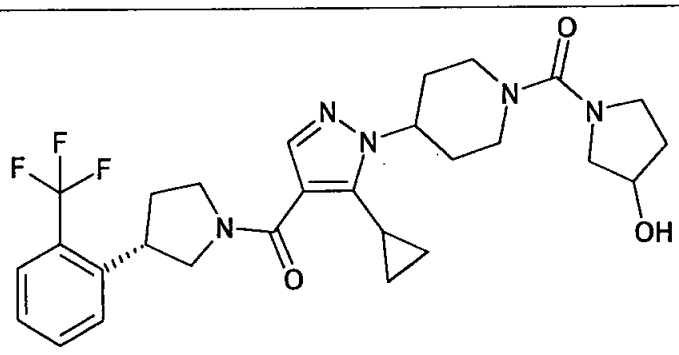
Ex. No.	structural formula	NMR
13		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.68-0.86 (2H,m), 1.00-1.15 (2H, m), 1.58-2.49 (15H, m), 2.84-3.03 (2H, m), 3.20-3.39 (2H,m), 3.41-4.25 (7H, m), 4.44-4.65 (1H, m), 5.13-5.29 (1H, m), 7.31-7.73 (5H, m)
14		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.82 (2H, m), 1.03-1.12 (2H, m), 1.46-1.60 (3H, m), 1.72-1.97 (5H, m), 2.00-2.44 (4H, m), 2.80-3.07 (4H, m), 3.42-4.10 (10H, m), 4.43-4.61 (1H, m), 7.32-7.71 (5H, m)
15		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.83 (2H, m), 1.02-1.14 (2H, m), 1.71-2.45 (9H, m), 2.81-2.96 (2H, m), 3.42-4.22 (11H, m), 4.45-4.63 (1H, m), 7.32-7.72 (5H, m)
16		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.66-0.85 (2H, m), 0.99-1.17 (2H, m), 1.71-2.45 (10H, m), 2.79-3.00 (2H, m), 3.27-4.11 (11H, m), 4.39-4.63 (2H, m), 7.32-7.73 (5H, m)

Table 1-5

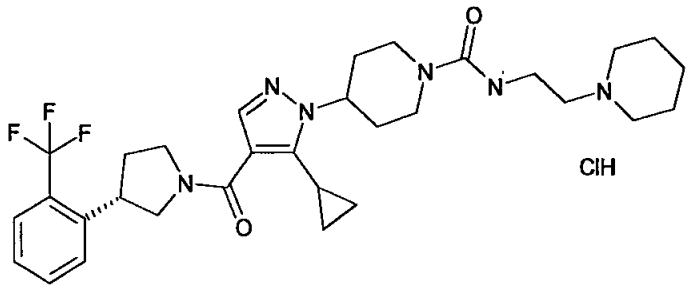
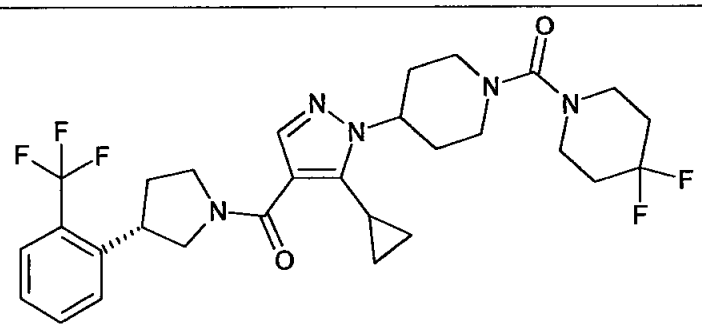
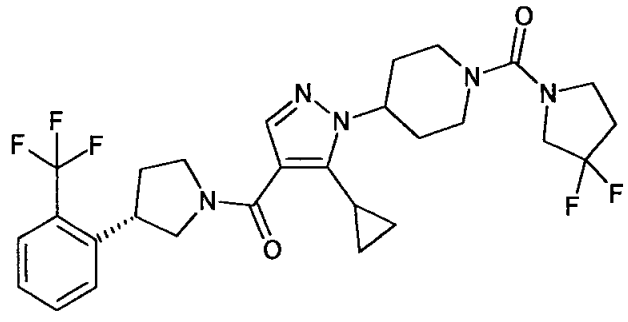
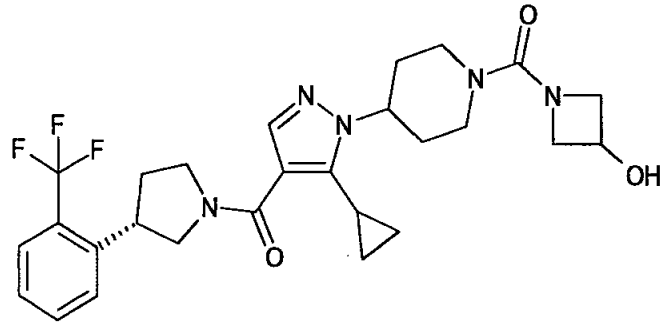
Ex. No.	structural formula	NMR
17		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.58-0.75 (2H, m), 0.92-1.06 (2H, m), 1.32-1.47 (1H, m), 1.63-1.98 (6H, m), 2.02-2.39 (2H,m), 2.78-3.00 (4H, m), 3.02-3.16 (2H, m), 3.38-3.54 (4H, m), 3.54-3.78 (3H, m), 3.80-4.55 (8H, m), 4.55-4.72 (1H, m), 7.01-7.20 (1H, brs), 7.41-7.60 (2H, m), 7.65-7.78 (3H, m), 9.99-10.16 (1H, brs)
18		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.86 (2H, m), 1.01-1.15 (2H, m), 1.71-2.45 (11H, m), 2.83-3.01 (2H, m), 3.33-3.51 (4H, m), 3.57-4.11 (7H, m), 4.45-4.62 (1H, m), 7.31-7.73 (5H, m)
19		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.86 (2H, m), 1.02-1.15 (2H, m), 1.70-2.46 (9H, m), 2.83-3.01 (2H, m), 3.41-4.12 (11H, m), 4.46-4.65 (1H, m), 7.31-7.73 (5H, m)
20		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.84 (2H, m), 1.00-1.16 (2H, m), 1.71-2.26 (6H, m), 2.27-2.45 (1H, m), 2.50-2.59 (1H, m), 2.81-3.00 (2H, m), 3.42-4.12 (9H, m), 4.46-4.68 (2H, m), 7.31-7.72 (5H, m)

Table 1-6

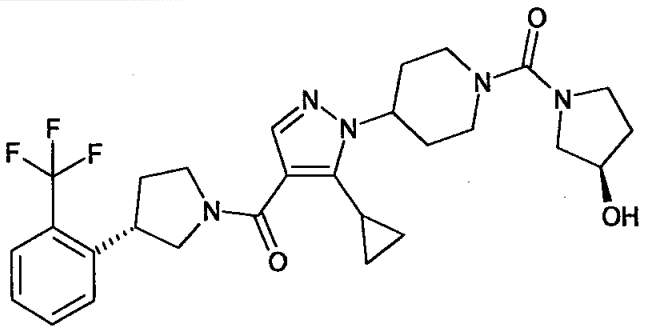
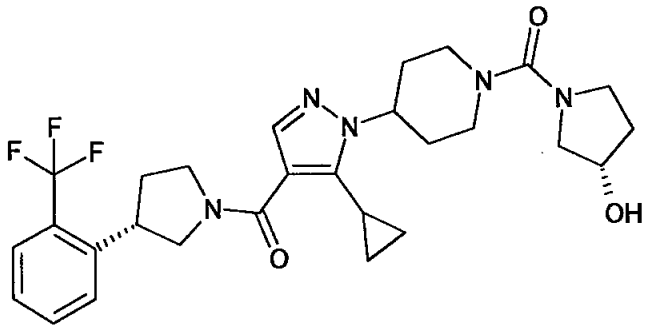
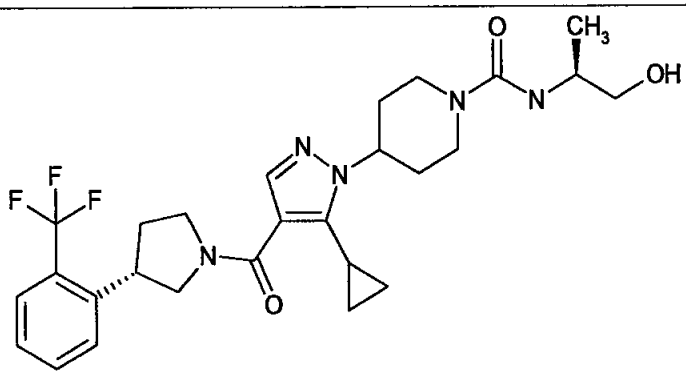
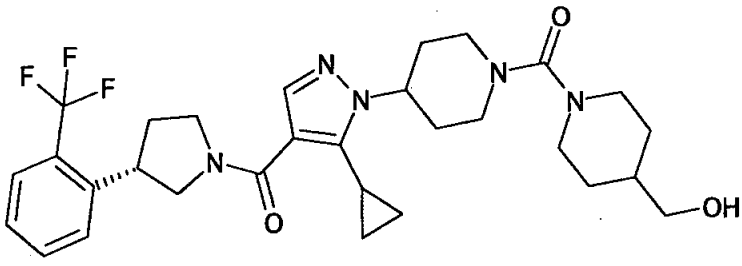
Ex. No.	structural formula	NMR
21		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.84 (2H, m), 0.99-1.15 (2H, m), 1.71-2.44 (10H, m), 2.78-2.99 (2H, m), 3.26-4.12 (11H, m), 4.42-4.62 (2H, m), 7.31-7.72 (5H, m)
22		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.85 (2H, m), 0.99-1.16 (2H, m), 1.68-2.47 (10H, m), 2.76-2.99 (2H, m), 3.27-4.11 (11H, m), 4.41-4.62 (2H, m), 7.32-7.73 (5H, m)
23		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.81 (2H,m), 1.05-1.15 (2H, m), 1.71-2.45 (7H, m), 1.94-2.44 (6H, m), 2.85-3.05 (2H, m), 3.35-4.20 (9H, m), 4.45-4.65 (1H, m), 4.65-4.75 (1H, m), 7.30-8.30 (5H, m)
24		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.83 (2H, m), 1.02-1.13 (2H, m), 1.15-1.32 (3H, m), 1.35-1.46 (1H, m), 1.63-2.45 (9H, m), 2.73-2.98 (4H, m), 3.40-4.12 (11H, m), 4.42-4.63 (1H, m), 7.29-7.74 (5H, m)

Table 1-7

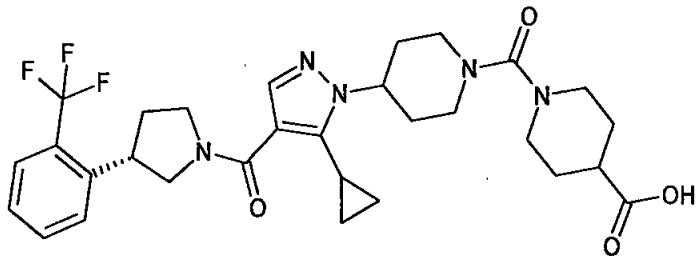
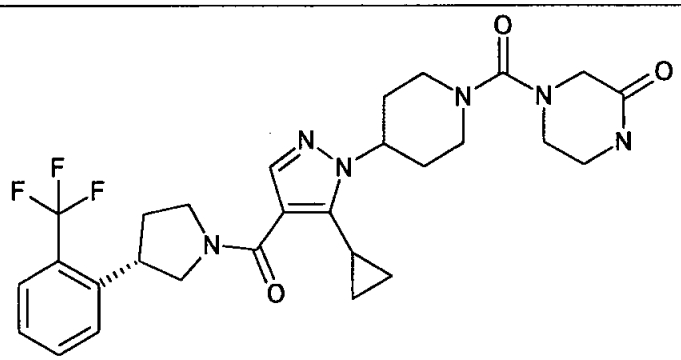
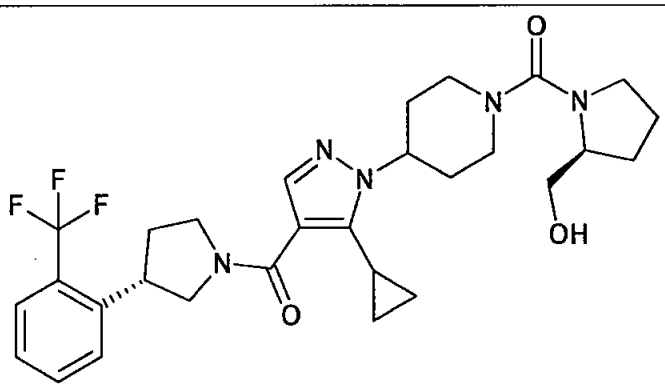
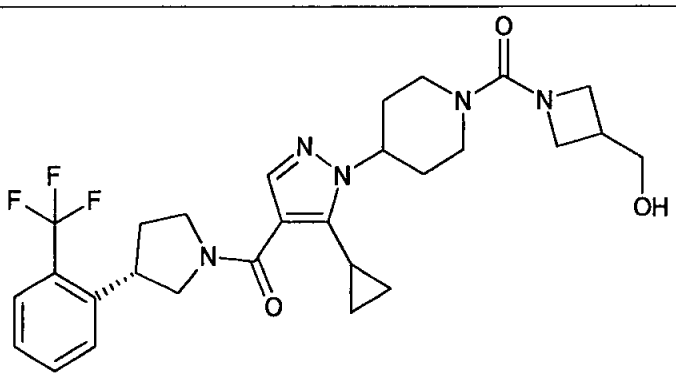
Ex. No.	structural formula	NMR
25		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.59-0.74 (2H, m), 0.91-1.06 (2H, m), 1.42-1.63 (2H, m), 1.72-2.46 (10H, m), 2.75-3.03 (4H, m), 3.43-3.96 (9H, m), 4.48-4.72 (1H, m), 7.38-7.83 (5H, m), 12.1-12.4 (1H, m)
26		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.66-0.85 (2H, m), 0.97-1.17 (2H, m), 1.68-2.46 (7H, m), 2.84-3.08 (2H, m), 3.36-4.13 (13H, m), 4.44-4.67 (1H, m), 6.54-6.71 (1H, m), 7.30-7.73 (5H, m)
27		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.84 (2H, m), 1.00-1.15 (2H, m), 1.43-1.59 (1H, m), 1.61-2.45 (10H, m), 2.78-3.01 (2H, m), 3.32-4.10 (11H, m), 4.18-4.31 (1H, m), 4.45-4.63 (1H, m), 7.31-7.72 (5H, m)
28		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.83 (2H, m), 0.96-1.16 (2H, m), 1.70-2.29 (6H, m), 2.29-2.39 (1H, m), 2.67-2.69 (1H, m), 2.82-2.97 (2H, m), 3.38-4.18 (13H, m), 4.41-4.65 (1H, m), 7.30-7.74 (5H, m)

Table 1-8

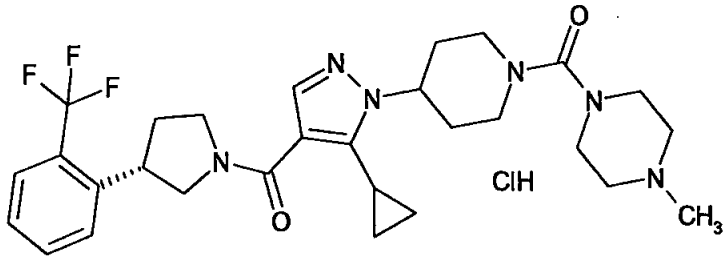
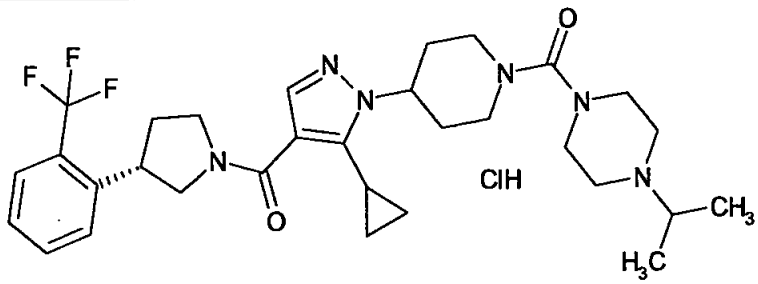
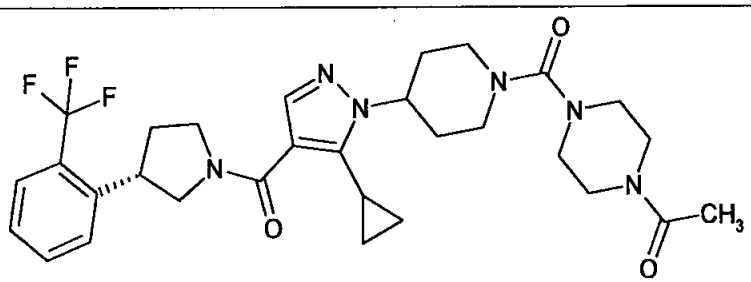
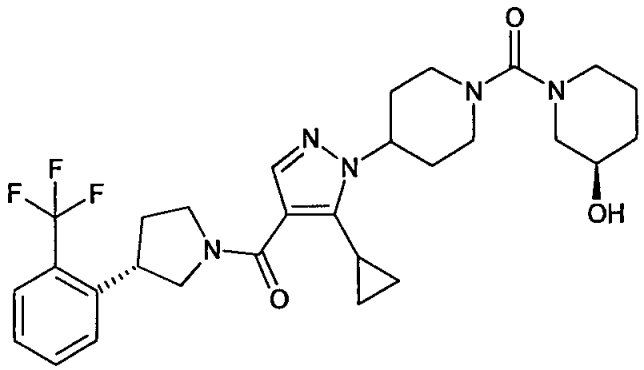
Ex. No.	structural formula	NMR
29		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.59-0.73 (2H, m), 0.94-1.06 (2H, m), 1.79-2.34 (7H, m), 2.74-2.82 (3H, m), 2.89-3.93 (17H, m), 4.55-4.74 (1H, m), 7.42-7.80 (5H, m), 10.4-10.6 (1H, m)
30		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.59-0.75 (2H, m), 0.92-1.06 (2H, m), 1.22-1.35 (6H, m), 1.77-2.46 (7H, m), 2.85-3.11 (5H, m), 3.21-3.96 (13H, m), 4.52-4.74 (1H, m), 7.42-7.82 (5H, m), 10.3-10.5 (1H, m)
31		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.85 (2H, m), 1.02-1.16 (2H, m), 1.71-2.47 (10H, m), 2.87-3.03 (2H, m), 3.20-4.15 (15H, m), 4.45-4.66 (1H, m), 7.31-7.73 (5H, m)
32		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.62-0.84 (2H, m), 0.97-1.15 (2H, m), 1.37-1.55 (1H, m), 1.55-1.96 (6H, m), 1.99-2.46 (5H, m), 2.77-3.03 (1H, m), 3.15-4.12 (12H, m), 4.38-4.65 (1H, m), 7.30-7.74 (5H, m)

Table 1-9

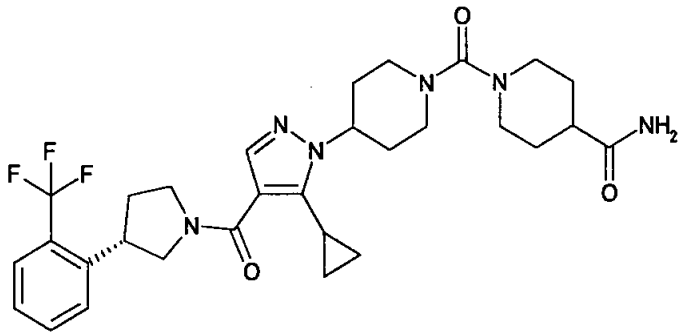
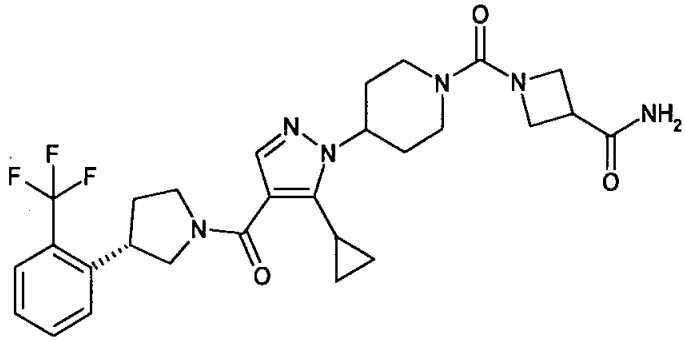
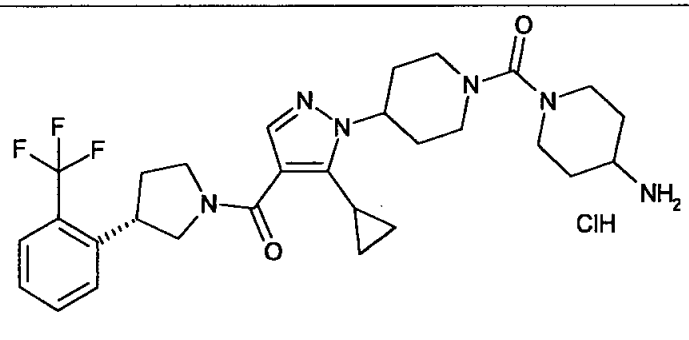
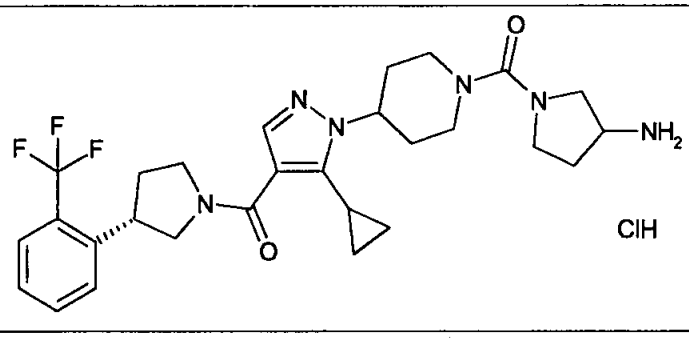
Ex. No.	structural formula	NMR
33		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.85 (2H, m), 1.01-1.14 (2H, m), 1.62-1.99 (7H, m), 1.99-2.47 (5H, m), 2.74-3.00 (4H, m), 3.41-3.53 (0.6H, m), 3.56-4.11 (8.4H, m), 4.43-4.61 (1H, m), 5.44 (1H, brs), 5.56 (1H, brs), 7.32-7.38 (1H, m), 7.39-7.60 (3H, m), 7.62-7.71 (1H, m)
34		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.83 (2H, m), 0.99-1.15 (2H, m), 1.67-1.96 (3H, m), 1.98-2.24 (3H, m), 2.25-2.44 (1H, m), 2.78-3.00 (2H, m), 3.20-3.39 (1H, m), 3.40-3.53 (0.5H, m), 3.53-4.09 (6.5H, m), 4.10-4.25 (4H, m), 4.40-4.66 (1H, m), 5.59 (1H, brs), 5.77 (1H, brs), 7.31-7.39 (1H, m), 7.40-7.60 (3H, m), 7.62-7.71 (1H, m)
35		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.59-0.72 (2H, m), 0.94-1.06 (2H, m), 1.39-1.56 (2H, m), 1.78-2.01 (6H, m), 2.05-2.34 (2H, m), 2.72-3.01 (4H, m), 3.24-3.27 (1H, m), 3.43-4.01 (9H, m), 4.53-4.70 (1H, m), 7.43-7.60 (2H, m), 7.66-7.77 (3H, m), 8.33 (3H, brs)
36		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.55-0.73 (2H, m), 0.89-1.08 (2H, m), 1.69-2.38 (10H, m), 2.77-3.02 (2H, m), 3.12-4.15 (11H, m), 4.52-4.73 (1H, m), 7.41-7.77 (3H, m), 8.18-8.40 (3H, m), 8.42-8.61 (1H, m), 9.36-9.63 (1H, m)

Table 1-10

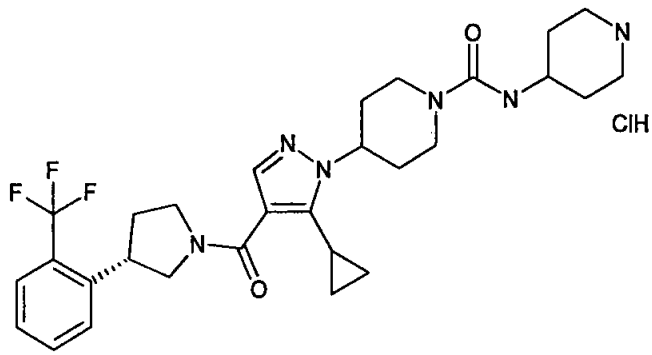
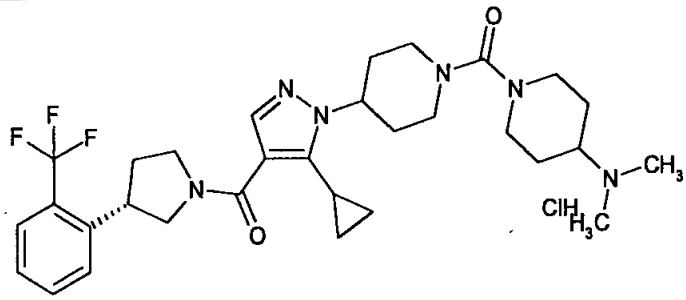
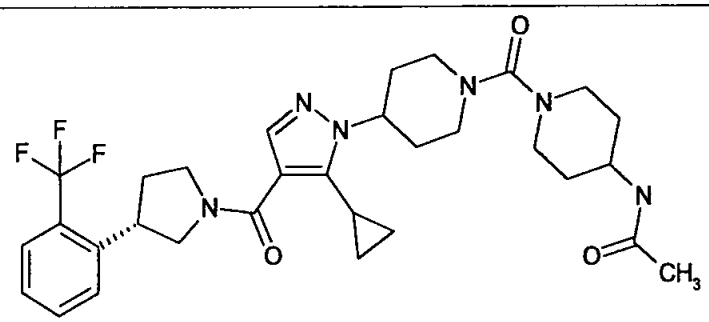
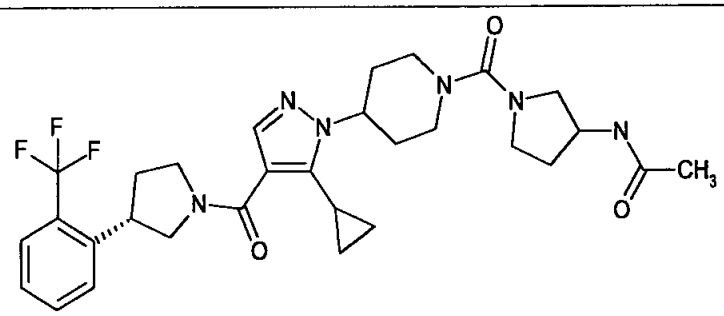
Ex. No.	structural formula	NMR
37		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.58-0.73 (2H, m), 0.92-1.04 (2H, m), 1.55-1.70 (2H, m), 1.74-1.98 (7H, m), 2.02-2.36 (2H, m), 2.73-3.02 (4H, m), 3.19-3.33 (2H, m), 3.45-4.32 (8H, m), 4.53-4.72 (1H, m), 6.44-6.62 (1H, m), 7.42-7.79 (5H, m), 8.62 (1H, br s), 8.72 (1H, br s)
38		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.58-0.74 (2H, m), 0.92-1.06 (2H, m), 1.47-1.68 (2H, m), 1.78-2.56 (8H, m), 2.62-3.03 (4H, m), 2.77 (6H, s), 3.24-3.94 (10H, m), 4.54-4.70 (1H, m), 7.42-7.62 (2H, m), 7.63-7.79 (3H, m), 10.2-10.4 (1H, m)
39		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.84 (2H, m), 1.02-1.14 (2H, m), 1.31-1.46 (2H, m), 1.71-2.45 (9H, m), 1.97 (3H, s), 2.81-3.00 (4H, m), 3.42-4.10 (10H, m), 4.44-4.61 (1H, m), 5.29-5.43 (1H, m), 7.33-7.72 (5H, m)
40		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.83 (2H, m), 1.00-1.13 (2H, m), 1.68-2.46 (13H, m), 2.81-3.00 (2H, m), 3.28-4.10 (10H, m), 4.36-4.63 (2H, m), 5.61-5.72 (1H, m), 7.31-7.70 (5H, m)

Table 1-11

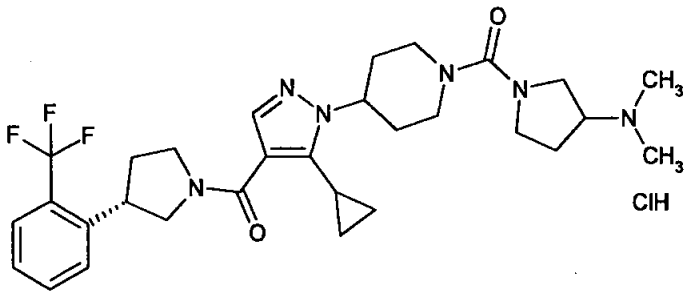
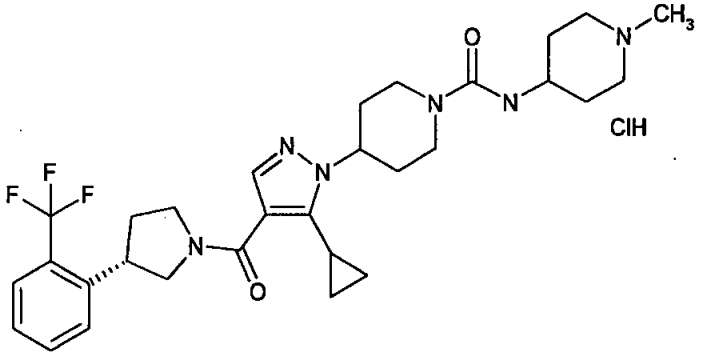
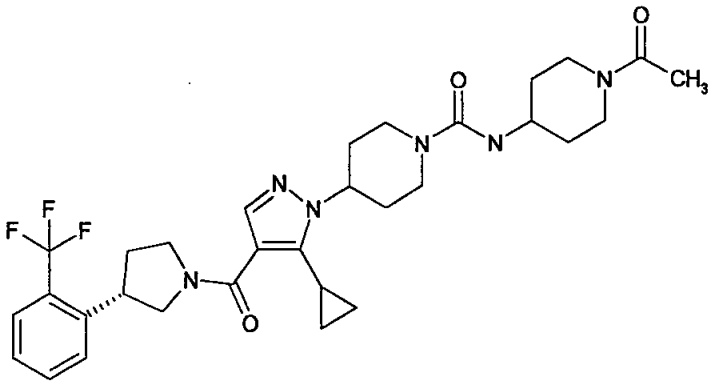
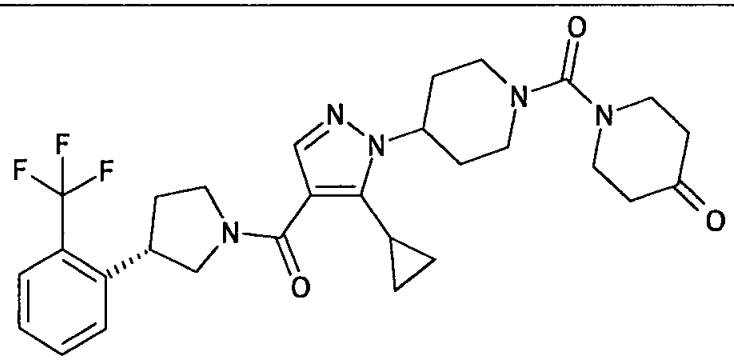
Ex. No.	structural formula	NMR
41		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.58-0.71 (2H, m), 0.92-1.03 (2H, m), 1.76-2.36 (8H, m), 2.70-2.80 (6H, brs), 2.81-3.03 (2H, m), 3.24-3.92 (13H, m), 4.52-4.71 (1H, m), 7.41-7.77 (5H, m), 10.76-10.91 (1H, brs)
42		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.58-0.74 (2H, m), 0.92-1.05 (2H, m), 1.60-2.00 (9H, m), 2.03-2.38 (2H, m), 2.65-3.93 (15H, m), 4.04-4.24 (2H, m), 4.51-4.73 (1H, m), 6.28-6.65 (1H, m), 7.41-7.81 (5H, m), 9.88 (1H, br s)
43		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.83 (2H, m), 1.02-1.15 (2H, m), 1.22-1.38 (2H, m), 1.70-2.26 (11H, m), 2.28-2.46 (1H, m), 2.67-2.79 (1H, m), 2.86-3.04 (2H, m), 3.10-3.24 (1H, m), 3.40-4.21 (9H, m), 4.32-4.45 (1H, m), 4.47-4.64 (2H, m), 7.32-7.72 (5H, m)
44		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.85 (2H, m), 1.02-1.18 (2H, m), 1.70-2.57 (11H, m), 2.91-3.08 (2H, m), 3.38-4.13 (11H, m), 4.74-4.66 (1H, m), 7.32-7.76 (5H, m)

Table 1-12

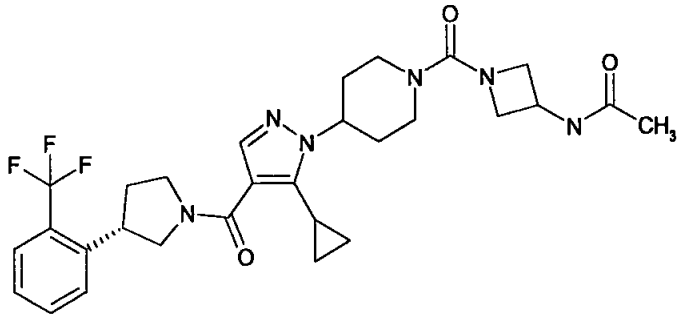
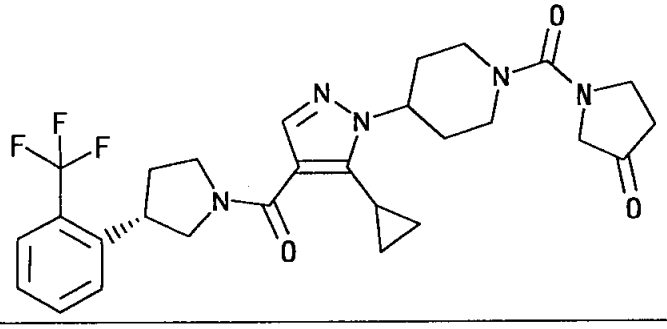
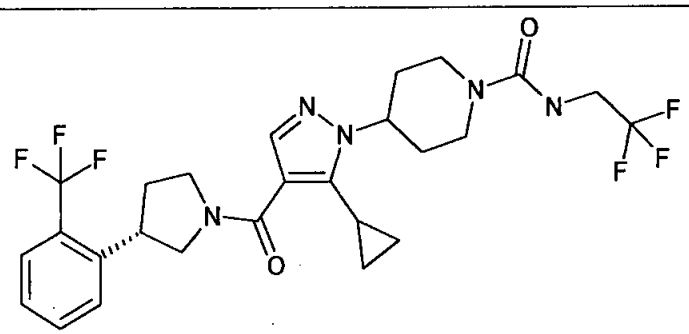
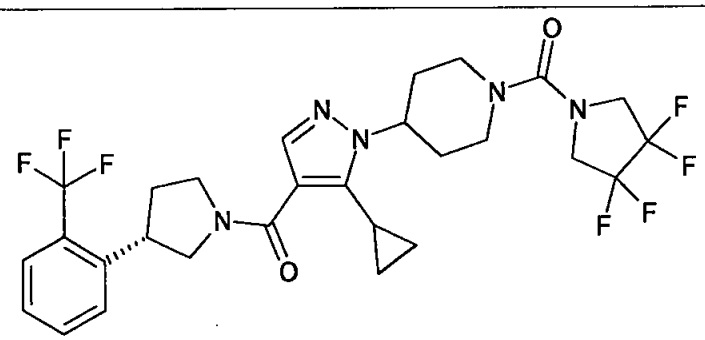
Ex. No.	structural formula	NMR
45		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.85 (2H, m), 0.96-1.17 (2H, m), 1.65-1.95 (3H, m), 1.96-2.22 (3H, m), 1.99 (3H, s), 2.25-2.48 (1H, m), 2.81-3.02 (2H, m), 3.38-3.5 (0.6H, m), 3.54-4.14 (8.4H, m), 4.19-4.37 (2H, m), 4.43-4.72 (2H, m), 6.24-6.40 (1H, m), 7.32-7.40 (1H, m), 7.41-7.61 (3H, m), 7.62-7.70 (1H, m)
46		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.88 (2H, m), 1.02-1.17 (2H, m), 1.71-1.87 (1H, m), 1.88-2.45 (6H, m), 2.48-2.60 (2H, m), 2.90-3.06 (2H, m), 3.43-4.11 (11H, m), 4.49-4.66 (1H, m), 7.33-7.72 (5H, m)
47		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.81 (2H, m), 1.01-1.12 (2H, m), 1.71-1.82 (1H, m), 1.83-1.96 (3H, m), 1.99-2.25 (3H, m), 2.26-2.43 (1H, m), 2.93-3.08 (2H, m), 3.41-4.00 (6H, m), 4.00-4.20 (2H, m), 4.49-4.64 (1H, m), 4.85-4.97 (1H, m), 7.30-7.70 (5H, m)
48		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.86 (2H, m), 1.01-1.17 (2H, m), 1.71-2.45 (7H, m), 2.86-3.06 (2H, m), 3.42-4.12 (11H, m), 4.49-4.67 (1H, m), 7.31-7.73 (5H, m)

Table 1-13

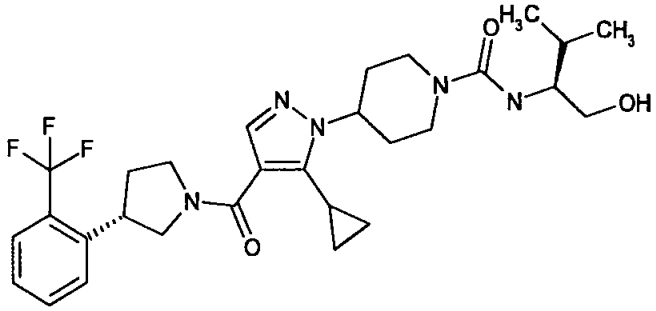
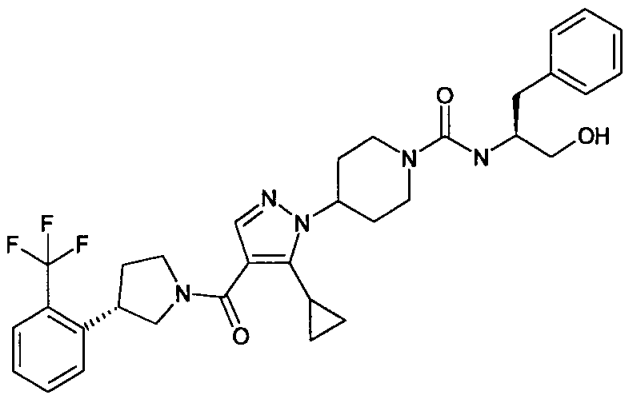
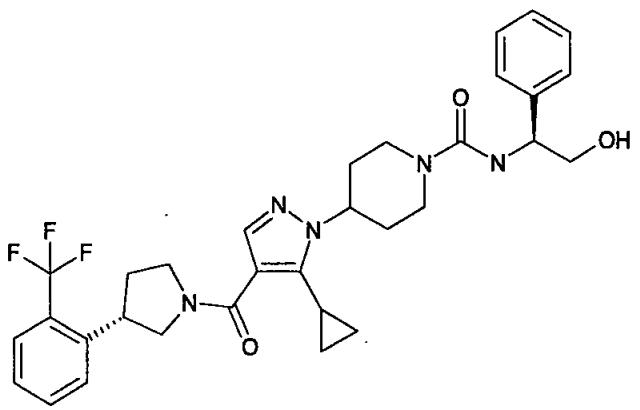
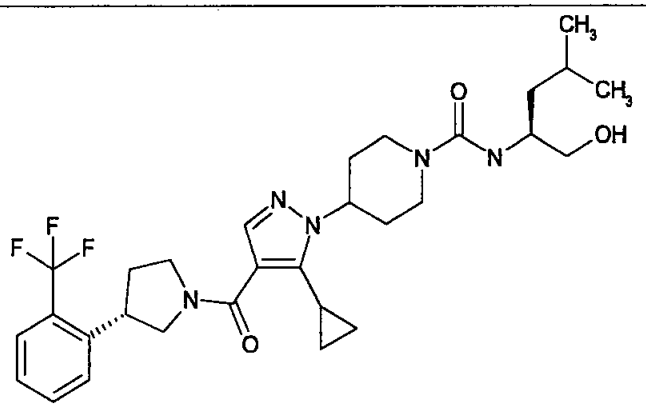
Ex. No.	structural formula	NMR
49		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.83 (2H,m), 0.92-1.02 (6H, m), 1.02-1.13 (2H, m), 1.22-1.33 (2H, m), 1.71-1.98 (4H,m), 1.99-2.45 (4H, m), 2.88-3.08 (2H, m), 3.14-3.28 (1H, brs), 3.38-4.24 (8H, m), 4.47-4.73 (2H, m), 7.32-7.72 (5H, m)
50		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.63-0.81 (2H, m), 0.96-1.13 (2H, m), 1.60-1.81 (3H, m), 1.90-2.21 (3H, m), 2.26-2.46 (1H, m), 2.72-2.98 (4H, m), 3.38-4.13 (9H, m), 4.37-4.59 (1H, m), 4.94-5.04 (1H, m), 7.16-7.73 (10H, m)
51		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.82 (2H, m), 1.00-1.12 (2H, m), 1.69-1.85 (3H, m), 1.96-2.22 (3H, m), 2.25-2.45 (1H, m), 2.84-3.01 (2H, m), 3.39-3.50 (2H, m), 3.54-4.27 (7H, m), 4.41-4.61 (1H, m), 4.93-5.04 (1H, m), 5.38-5.55 (1H, m), 7.23-7.73 (10H, m)
52		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.79 (2H, m), 0.89-0.99 (6H, m), 1.02-1.12 (2H, m), 1.31-1.43 (2H, m), 1.60-1.85 (4H, m), 2.00-2.20 (3H, m), 2.25-2.45 (1H, m), 2.81-3.00 (2H, m), 3.39-4.21 (10H, m), 4.42-4.60 (1H, m), 4.79-4.92 (1H, m), 7.30-7.73 (5H, m)

Table 1-14

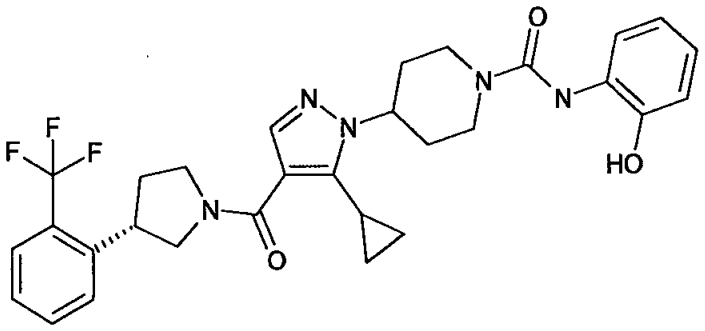
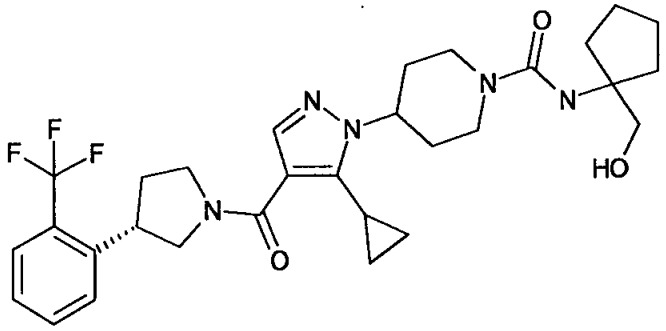
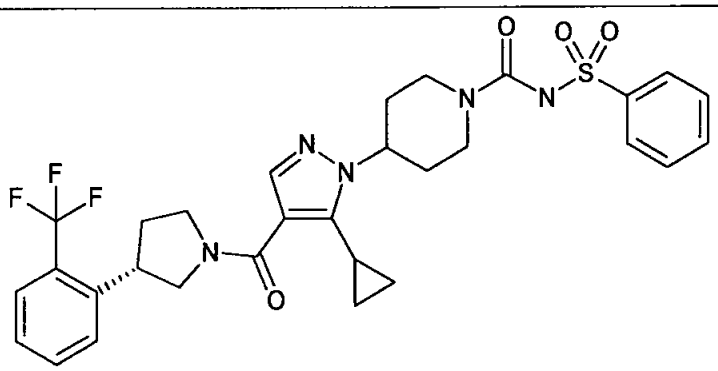
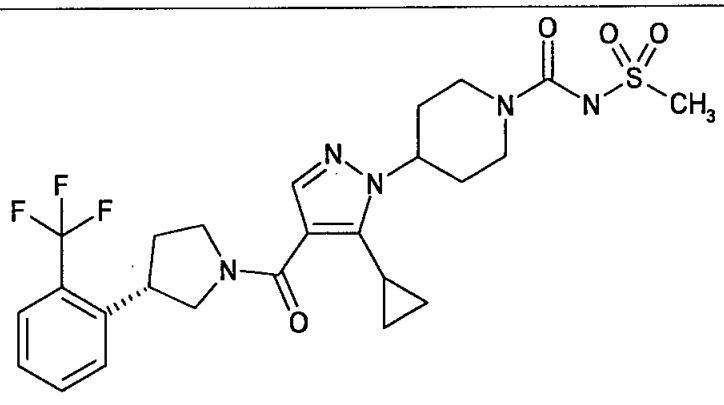
Ex. No.	structural formula	NMR
53		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.66-0.83 (2H, m), 1.00-1.14 (2H, m), 1.67-1.90 (3H, m), 1.98-2.27 (3H, m), 2.27-2.24 (1H, m), 2.98-3.14 (2H, m), 3.42-4.11 (5H, m), 4.22-4.40 (2H, m), 4.50-4.66 (1H, m), 6.78-6.88 (1H, m), 6.98-7.13 (3H, m), 7.14-7.21 (1H, m), 7.34-7.61 (4H, m), 7.64-7.73 (1H, m), 9.24-9.36 (1H, m)
54		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.85 (2H, m), 0.97-1.16 (2H, m), 1.51-2.46 (15H, m), 2.84-3.07 (2H, m), 3.42-4.19 (9H, m), 4.47-4.64 (1H, m), 4.65-4.75 (1H, m), 5.14-5.24 (1H, m), 7.31-7.73 (5H, m)
55		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.61-0.85 (2H, m), 0.95-1.18 (2H, m), 1.36-2.25 (7H, m), 2.25-2.44 (1H, m), 2.76-3.05 (2H, m), 3.38-3.47 (0.5H, m), 3.52-3.91 (3.5H, m), 3.95-4.31 (3H, m), 4.34-4.60 (1H, m), 7.29-7.73 (8H, m), 8.00-8.13 (2H, m)
56		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.63-0.83 (2H, m), 0.98-1.16 (2H, m), 1.65-1.91 (3H, m), 1.92-2.23 (3H, m), 2.24-2.50 (1H, m), 2.80-3.05 (2H, m), 3.16-3.34 (3H, m), 3.39-3.51 (0.6H, m), 3.52-4.13 (5.4H, m), 4.19-4.43 (2H, m), 4.44-4.64 (1H, m), 7.30-7.39 (1H, m), 7.41-7.60 (3H, m), 7.61-7.70 (1H, m)

Table 1-15

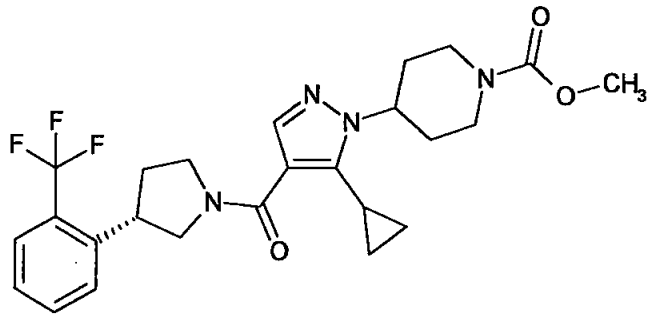
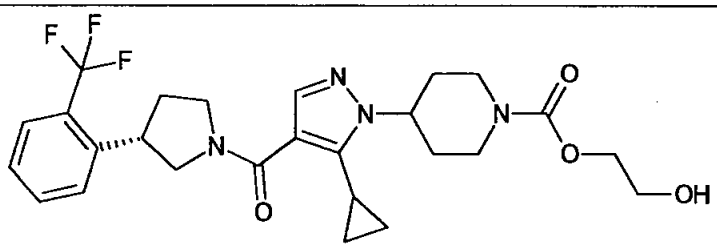
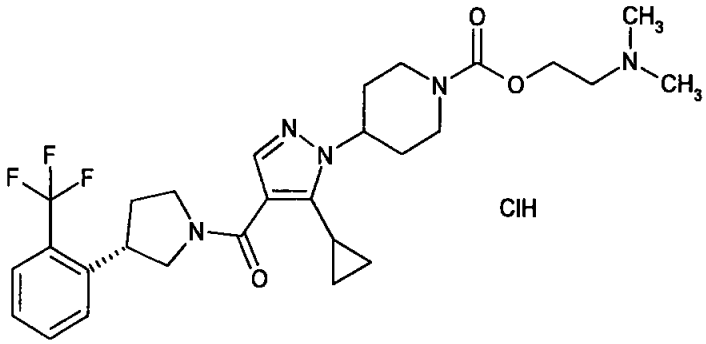
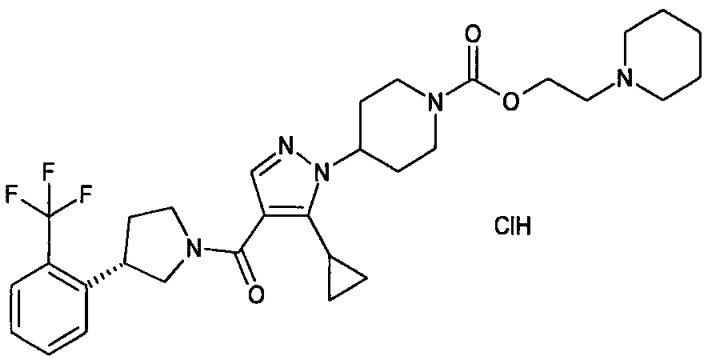
Ex. No.	structural formula	NMR
57		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.83 (2H, m), 0.98-1.15 (2H, m), 1.65-1.94 (3H, m), 1.94-2.25 (3H,m), 2.25-2.45 (1H, m), 2.77-3.05 (2H, m), 3.43-4.07 (8H, m), 4.11-4.45 (2H, m), 4.45-4.65 (1H, m), 7.30-7.72 (5H, m)
58		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.67-0.84 (2H, m), 1.03-1.15 (2H, m), 1.69-2.59 (8H, m), 2.86-3.11 (2H, m), 3.38-4.13 (7H, m), 4.19-4.44 (4H, m), 4.48-4.66 (1H, m), 7.30-7.74 (5H, m)
59		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.87 (2H, m), 0.99-1.18 (2H, m), 1.72-1.86 (1H, m), 1.87-1.99 (2H, m), 2.06-2.47 (4H, m), 2.63-3.23 (10H, m), 3.26-3.42 (2H, m), 3.43-4.13 (3H, m), 4.20-4.75 (5H, m), 7.33-7.39 (1H, m), 7.40-7.63 (3H, m), 7.64-7.69 (1H, m), 12.69 (1H, brs)
60		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.72-0.83 (2H, m), 1.07-1.23 (2H, m), 1.35-1.56 (1H, m), 1.79-2.00 (4H, m), 2.06-2.45 (6H, m), 2.68-3.20 (4H, m), 3.27-3.41 (2H, m), 3.43-4.08 (9H, m), 4.22-4.48 (2H, m), 4.58-4.82 (3H, m), 7.34-7.40 (1H, m), 7.44-7.50 (1H, m), 7.53-7.60 (1H, m), 7.65-7.72 (2H, m), 12.22 (1H, brs)

Table 1-16

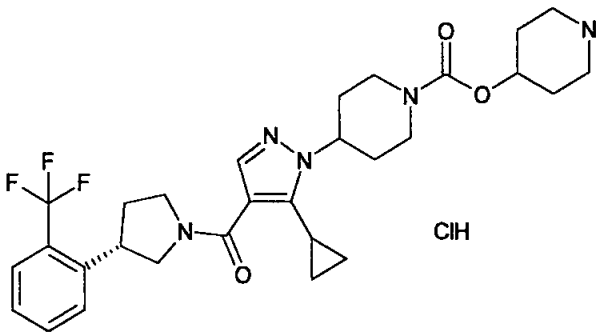
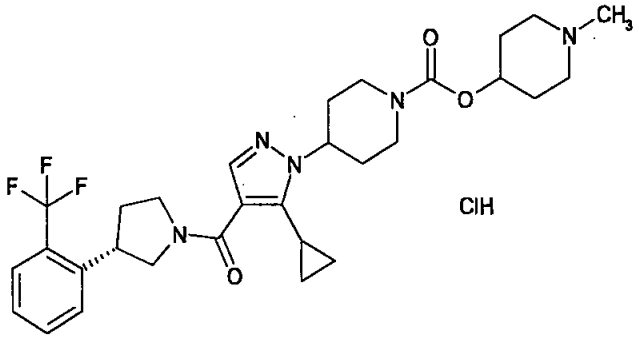
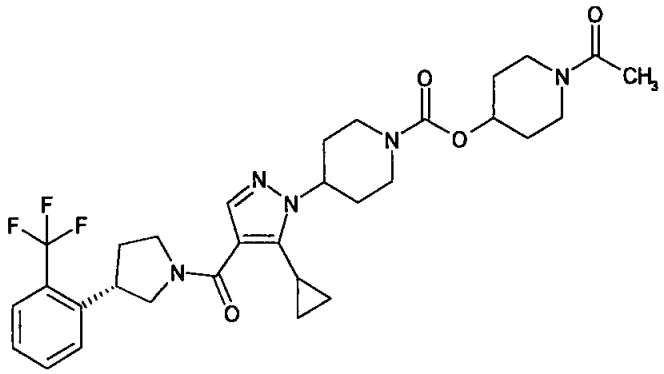
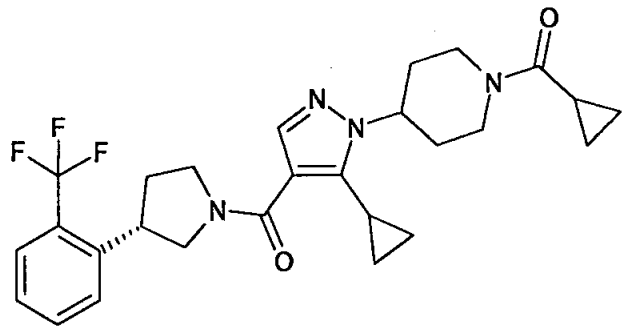
Ex. No.	structural formula	NMR
61		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.88 (2H, m), 1.03-1.21 (2H, m), 1.79-2.01 (3H, m), 2.01-2.32 (7H, m), 2.33-2.45 (1H, m), 2.81-3.12 (2H, m), 3.11-4.14 (9H, m), 4.15-4.49 (2H, m), 4.54-4.75 (1H, m), 4.92-5.09 (1H, m), 7.33-7.41 (1H, m), 7.44-7.61 (2H, m), 7.63-7.75 (2H, m), 9.45-9.81 (2H, m)
62		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.87 (2H, m), 1.04-1.21 (2H, m), 1.78-2.01 (3H, m), 2.03-2.49 (7H, m), 2.50-2.68 (1H, m), 2.72-3.14 (7H, m), 3.23-4.07 (7H, m), 4.17-4.44 (2H, m), 4.57-4.75 (1H, m), 4.76-4.89 (0.5H, m), 5.01-5.09 (0.5H, m), 7.33-7.41 (1H, m), 7.43-7.52 (1H, m), 7.52-7.61 (1H, m), 7.62-7.73 (2H, m), 12.38-12.70 (1H, m)
63		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.66-0.85 (2H, m), 0.99-1.16 (2H, m), 1.57-2.25 (13H, m), 2.26-2.46 (1H, m), 2.79-3.11 (2H, m), 3.27-3.54 (2.6H, m), 3.55-4.12 (6.4H, m), 4.14-4.66 (3H, m), 4.85-5.00 (1H, m), 7.31-7.40 (1H, m), 7.41-7.61 (3H, m), 7.62-7.71 (1H, m)
64		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.87 (4H, m), 0.91-1.18 (4H, m), 1.70-1.86 (2H, m), 1.88-2.48 (6H, m), 2.65-2.89 (1H, m), 3.13-3.39 (1H, m), 3.41-4.13 (5H, m), 4.27-4.89 (3H, m), 7.31-7.76 (5H, m)

Table 1-17

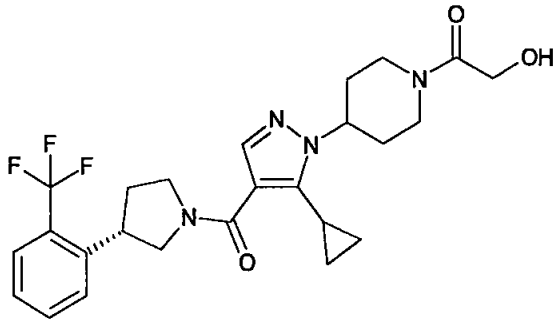
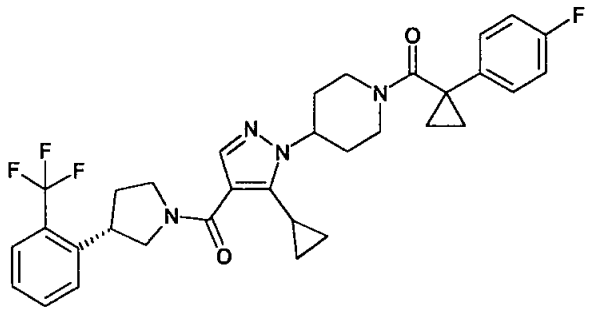
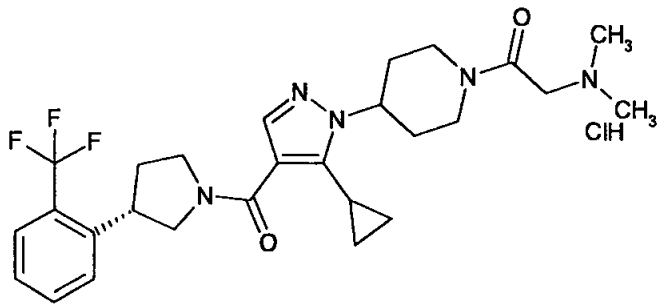
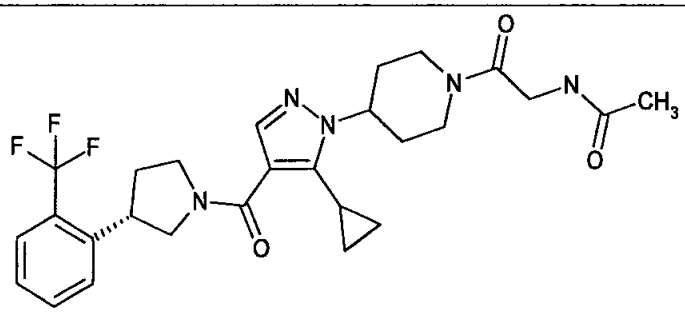
Ex. No.	structural formula	NMR
65		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.87 (2H, m), 1.01-1.16 (2H, m), 1.69-1.86 (1H, m), 1.90-2.49 (6H, m), 2.85-3.02 (1H, m), 3.07-3.26 (1H, m), 3.40-4.12 (7H, m), 4.16-4.29 (2H, m), 4.54-4.82 (2H, m), 7.31-7.77 (5H, m)
66		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.63-0.83 (2H, m), 0.98-1.10 (2H, m), 1.12-1.23 (2H, m), 1.38-1.51 (2H, m), 1.66-2.22 (6H, m), 2.27-2.45 (1H, m), 2.73-3.03 (2H, m), 3.37-4.11 (5H, m), 4.15-4.95 (3H, m), 6.94-7.73 (9H, m)
67		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.74 (2H, m), 0.92-1.06 (2H, m), 1.15-1.20 (1H, m), 1.75-2.36 (4H, m), 2.78-2.87 (6H, brs), 3.14-3.36 (1H, m), 3.40-3.92 (9H, m), 4.22-4.56 (3H, m), 4.64-4.86 (1H, m), 7.40-7.62 (2H, m), 7.64-7.77 (3H, m), 9.61-9.74 (1H, brs)
68		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.72-0.84 (2H, m), 1.04-1.16 (2H, m), 1.72-1.86 (1H, m), 1.90-2.28 (8H, m), 2.28-2.45 (1H, m), 2.81-2.96 (1H, m), 3.15-3.29 (1H, m), 3.42-3.51 (0.5H, m), 3.58-4.21 (7.5H, m), 4.58-4.79 (2H, m), 6.58-6.67 (1H, br s), 7.33-7.42 (1H, m), 7.42-7.62 (3H, m), 7.63-7.72 (1H, m)

Table 1-18

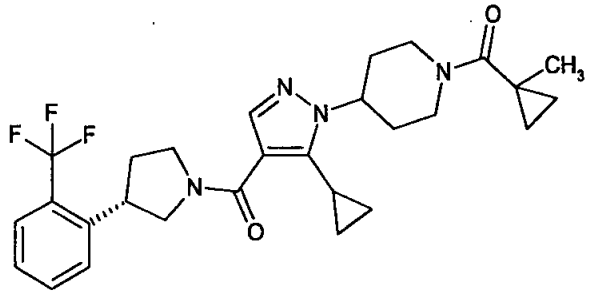
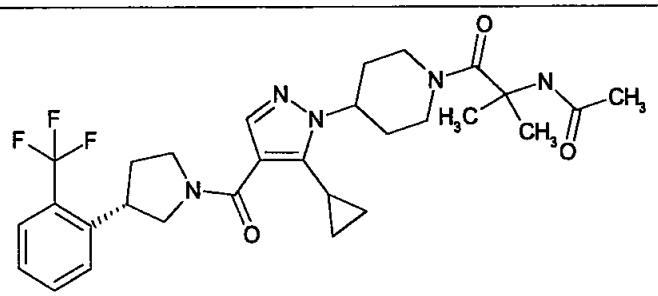
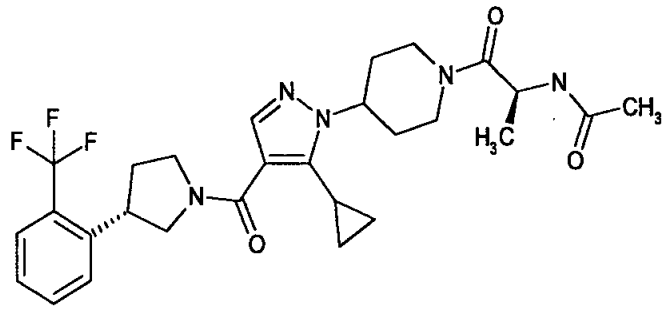
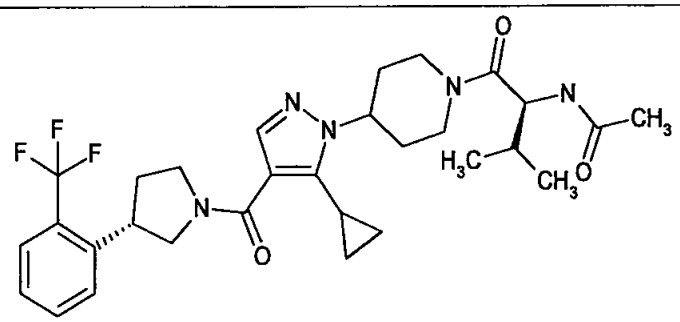
Ex. No.	structural formula	NMR
69		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.54-0.67 (2H, m), 0.71-0.86 (2H, m), 0.92-1.02 (2H, m), 1.04-1.14 (2H, m), 1.28-1.40 (3H, m), 1.72-1.86 (1H, m), 1.89-2.24 (5H, m), 2.27-2.46 (1H, m), 2.86-3.13 (2H, m), 3.41-4.12 (5H, m), 4.51-4.71 (3H, m), 7.32-7.75 (5H, m)
70		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.82 (2H, m), 1.01-1.12 (2H, m), 1.60-1.71 (7H, m), 1.71-2.45 (10H, m), 2.93-3.12 (1H, m), 3.37-4.10 (6H, m), 4.47-4.70 (2H, m), 6.70-6.79 (1H, brs), 7.28-7.71 (5H, m)
71		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.84 (2H, m), 1.02-1.13 (2H, m), 1.29-1.41 (4H, m), 1.71-1.84 (1H, m), 1.89-2.45 (7H, m), 2.76-2.96 (2H, m), 3.16-3.34 (2H, m), 3.39-4.15 (5H, m), 4.56-4.79 (2H, m), 4.85-4.99 (1H, m), 6.55-6.67 (1H, m), 7.31-7.70 (5H, m)
72		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.83 (2H, m), 0.84-1.03 (6H, m), 1.03-1.14 (2H, m), 1.22-1.34 (2H, m), 1.71-2.44 (9H, m), 2.76-2.92 (1H, m), 3.17-4.79 (9H, m), 4.84-4.95 (1H, m), 6.19-6.30 (1H, m), 7.31-7.71 (5H, m)

Table 1-19

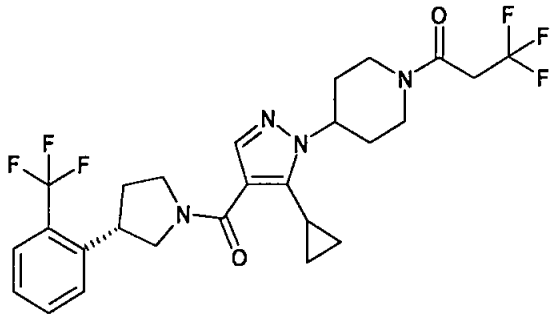
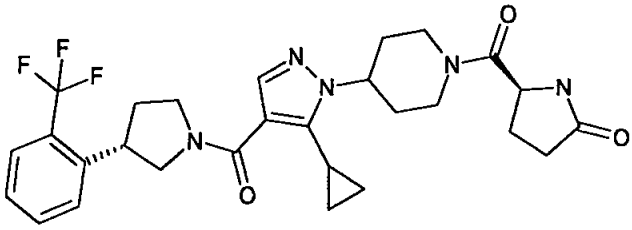
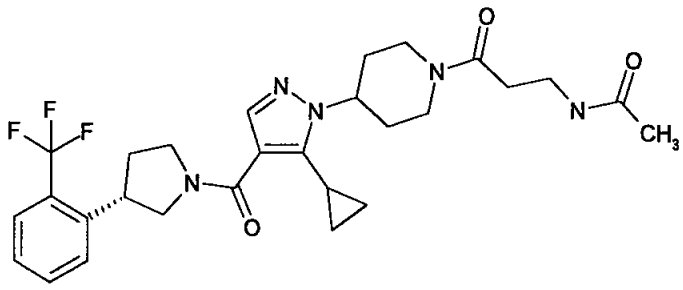
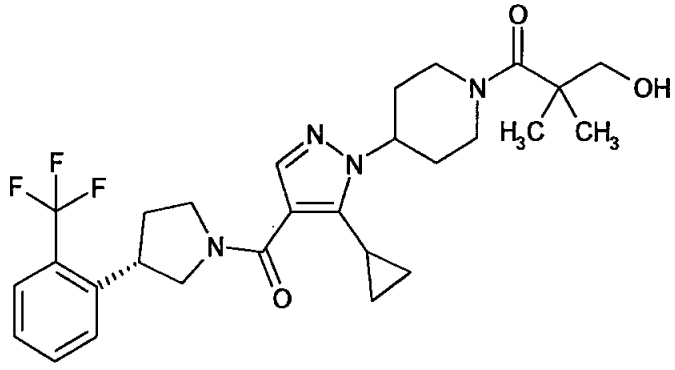
Ex. No.	structural formula	NMR
73		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.66-0.86 (2H, m), 0.99-1.18 (2H, m), 1.69-1.85 (1H, m), 1.89-2.45 (6H, m), 2.78-2.94 (1H, m), 3.19-3.39 (3H, m), 3.41-3.50 (0.6H, m), 3.56-4.10 (5.4H, m), 4.56-4.83 (2H, m), 7.32-7.40 (1H, m), 7.41-7.61 (3H, m), 7.62-7.71 (1H, m)
74		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.85 (2H, m), 1.03-1.15 (2H, m), 1.69-1.86 (1H, m), 1.91-2.61 (9H, m), 2.76-2.95 (1H, m), 3.18-4.11 (8H, m), 4.44-4.83 (3H, m), 5.76-5.93 (1H, m), 7.32-7.75 (5H, m)
75		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.82 (2H, m), 1.02-1.13 (2H, m), 1.69-1.84 (1H, m), 1.85-2.01 (6H, m), 2.02-2.23 (2H, m), 2.26-2.46 (1H, m), 2.47-2.60 (2H, m), 2.71-2.84 (1H, m), 3.11-3.26 (1H, m), 3.41-4.10 (8H, m), 4.54-4.68 (1H, m), 4.69-4.82 (1H, m), 6.32-6.40 (1H, brs), 7.31-7.70 (5H, m)
76		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.87 (2H, m), 1.02-1.18 (2H, m), 1.31 (3H, s), 1.33 (3H, s), 1.72-1.88 (1H, m), 1.90-2.48 (6H, m), 2.88-3.10 (2H, m), 3.42-4.15 (8H, m), 4.47-4.75 (3H, m), 7.32-7.74 (5H, m)

Table 1-20

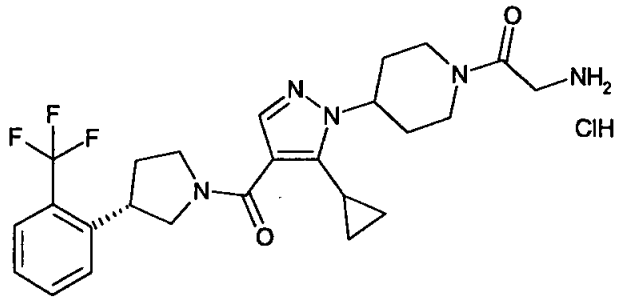
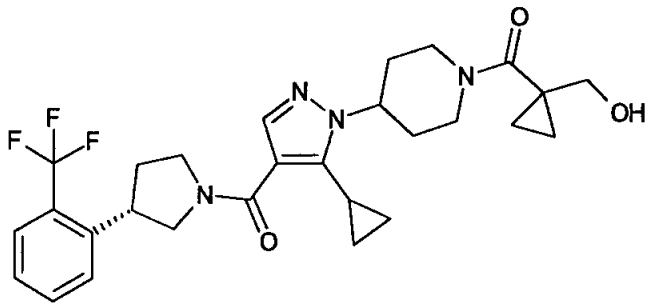
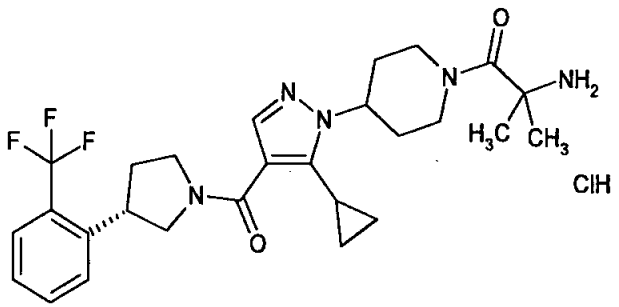
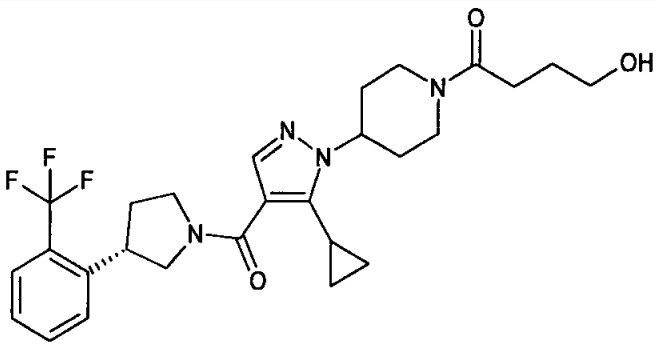
Ex. No.	structural formula	NMR
77		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.59-0.74 (2H, m), 0.93-1.05 (2H, m), 1.21-1.32 (1H, m), 1.72-2.34 (5H, m), 2.79-2.98 (1H,m), 3.13-3.34 (1H, m), 3.39-4.36 (9H, m), 4.38-4.55 (1H, m), 4.63-4.84 (1H, m), 7.40-7.60 (2H, m), 7.63-7.74 (3H, m), 8.80-8.18 (3H, brs)
78		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.89 (4H, m), 0.97-1.16 (4H, m), 1.71-1.86 (1H, m), 1.88-2.24 (6H, m), 2.27-2.46 (1H, m), 2.90-3.11 (2H, m), 3.41-4.11 (7H, m), 4.54-4.74 (3H, m), 7.33-7.74 (5H, m)
79		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.74 (2H, m), 0.94-1.03 (2H, m), 1.50-1.65 (7H, m), 1.74-2.38 (5H, m), 2.99-3.28 (2H,m), 3.37-3.90 (5H, m), 3.94-4.65 (3H, m), 4.67-4.89 (1H, m), 7.40-7.78 (5H, m), 8.12-8.32 (3H, brs)
80		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.83 (2H, m), 1.02-1.14 (2H, m), 1.70-1.85 (1H, m), 1.85-2.46 (8H, m), 2.49-2.60 (2H, m), 2.69-2.85 (2H, m), 3.13-3.29 (1H, m), 3.41-3.50 (0.5H, m), 3.55-4.14 (7.5H, m), 4.53-4.70 (1H, m), 4.71-4.85 (1H, m), 7.31-7.40 (1H, m), 7.40-7.61 (3H, m), 7.62-7.73 (1H, m)

Table 1-21

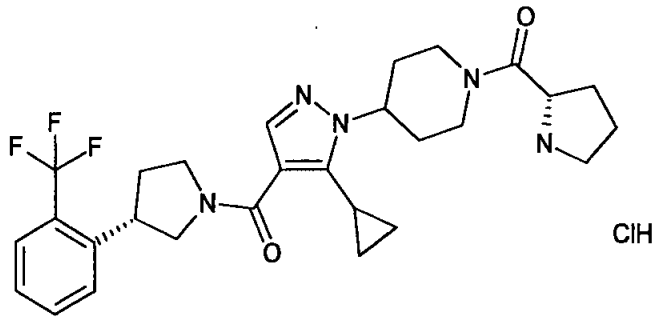
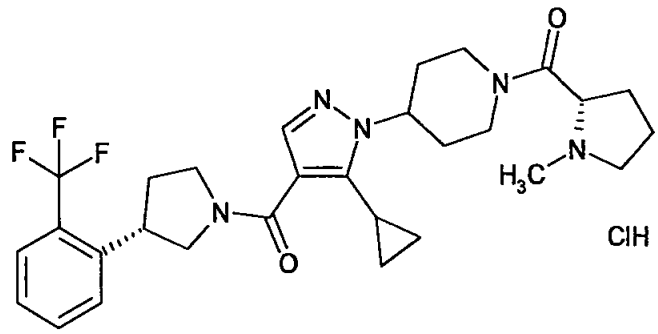
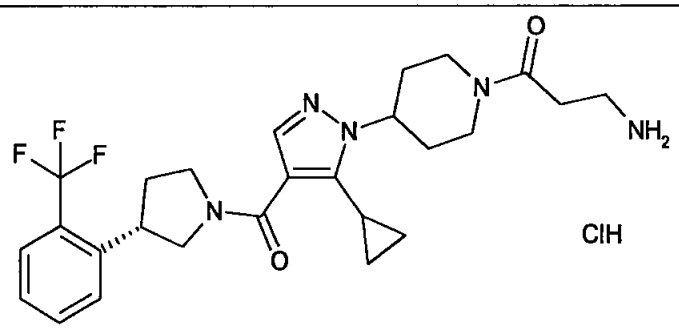
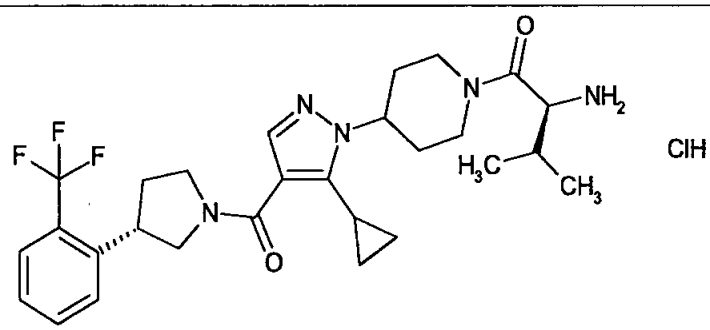
Ex. No.	structural formula	NMR
81		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.58-0.74 (2H, m), 0.93-1.10 (2H, m), 1.70-2.48 (12H, m), 2.83-3.03 (1H, m), 3.11-4.08 (9H, m), 4.41-4.85 (2H, m), 7.42-7.53 (2H, m), 7.65-7.78 (3H, m), 9.91-10.05 (1H, brs), 10.12-10.24 (1H, brs)
82		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.75 (2H, m), 0.92-1.03 (2H, m), 1.74-2.17 (11H, m), 2.18-2.35 (1H, m), 2.73-2.87 (3H, m), 2.88-3.90 (10H, m), 4.43-4.56 (1H, m), 4.60-4.85 (1H, m), 7.41-7.76 (5H, m), 9.53-9.70 (1H, brs)
83		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.58-0.72 (2H, m), 0.93-1.04 (2H, m), 1.69-2.02 (5H, m), 2.03-2.16 (1H, m), 2.17-2.34 (1H, m), 2.64-2.87 (3H, m), 2.91-3.07 (2H, m), 3.16-3.32 (1H, m), 3.42-3.78 (6H, m), 3.80-3.99 (1H, m), 4.44-4.58 (1H, m), 7.42-7.94 (8H, m)
84		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.73 (2H, m), 0.87-1.10 (8H, m), 1.73-2.17 (8H, m), 2.18-2.34 (1H, m), 2.81-2.98 (1H, m), 3.21-3.37 (1H, m), 3.40-3.92 (4H, m), 4.04-4.19 (1H, m), 4.23-4.41 (1H, m), 4.46-4.61 (1H, m), 4.66-4.85 (1H, m), 7.43-7.61 (2H, m), 7.64-7.77 (3H, m), 8.07-8.24 (3H, m)

Table 1-22

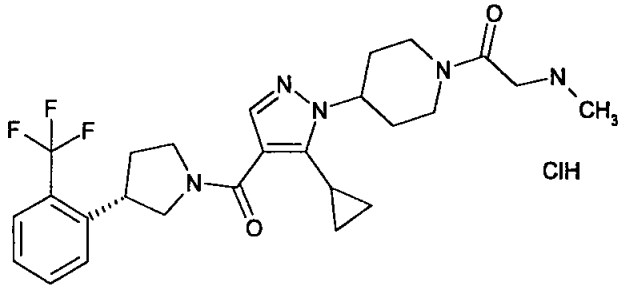
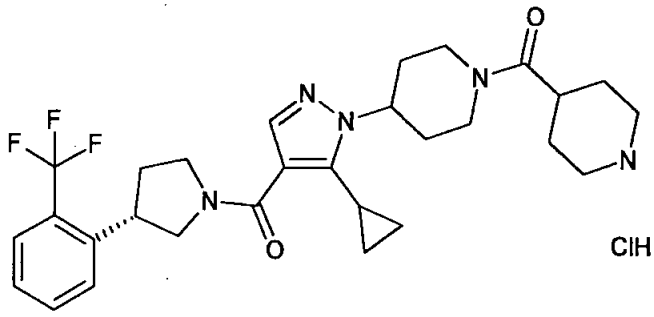
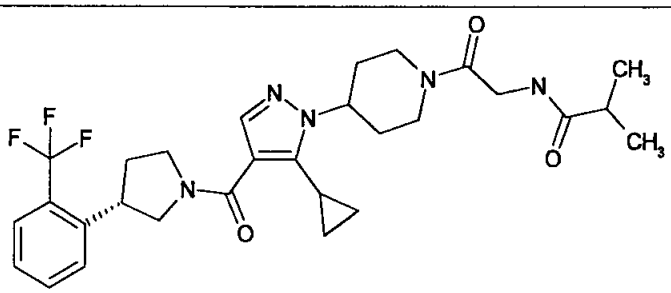
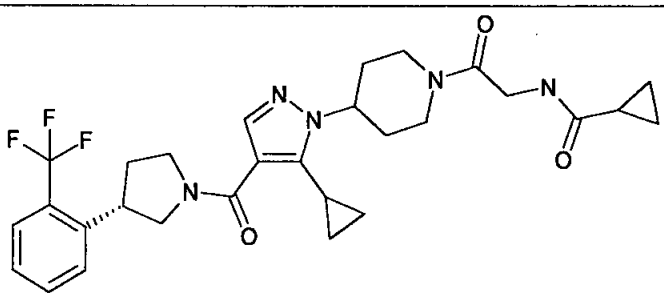
Ex. No.	structural formula	NMR
85		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.74 (2H, m), 0.92-1.06 (2H, m), 1.72-2.35 (8H, m), 2.53-2.62 (3H, m), 2.80-2.98 (1H, m), 3.18-3.34 (1H, m), 3.42-3.90 (5H, m), 3.98-4.23 (2H, m), 4.40-4.54 (1H, m), 4.66-4.82 (1H, m), 7.42-7.78 (5H, m), 8.77-9.02 (2H, m)
86		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.59-0.72 (2H, m), 0.93-1.02 (2H, m), 1.67-1.84 (6H, m), 1.85-2.00 (4H, m), 2.03-2.17 (1H, m), 2.18-2.33 (1H, m), 2.65-2.81 (1H, m), 2.84-3.08 (3H, m), 3.16-3.32 (4H, m), 3.52-3.90 (3H, m), 4.05-4.19 (1H, m), 4.44-4.57 (1H, m), 4.63-4.79 (1H, m), 7.40-7.75 (5H, m), 8.62-8.78 (1H, m), 9.04-9.16 (1H, m)
87		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.84 (2H, m), 1.03-1.12 (2H, m), 1.14-1.22 (7H, m), 1.66-2.24 (6H, m), 2.27-2.54 (2H, m), 2.79-2.96 (1H, m), 3.13-3.27 (1H, m), 3.39-3.50 (1H, m), 3.55-4.18 (6H, m), 4.53-4.79 (2H, m), 6.58-6.61 (1H, m), 7.31-7.71 (5H, m)
88		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.83 (4H, m), 0.92-1.01 (2H, m), 1.01-1.13 (2H, m), 1.45-1.54 (1H, m), 1.68-2.44 (8H, m), 2.80-2.95 (1H, m), 3.12-3.29 (1H, m), 3.41-3.50 (1H, m), 3.57-4.22 (6H, m), 4.56-4.79 (2H, m), 6.68-6.76 (1H, m), 7.31-7.70 (5H, m)

Table 1-23

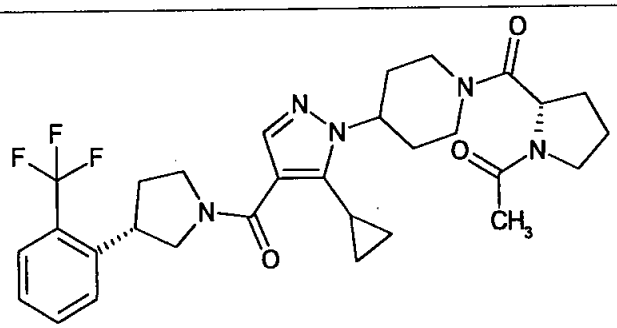
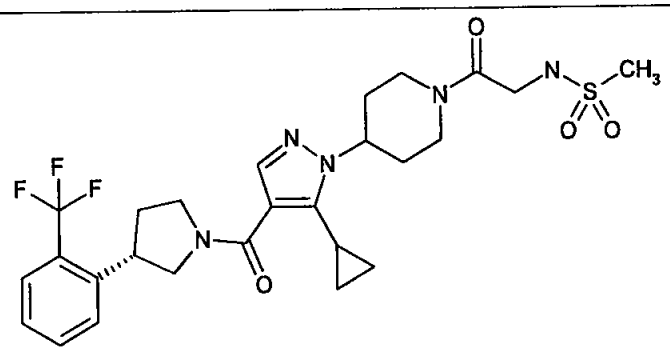
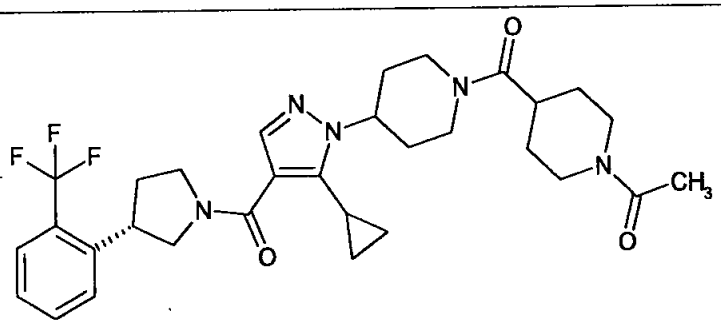
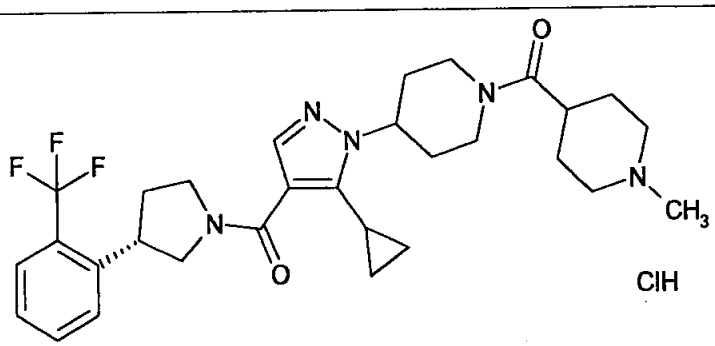
Ex. No.	structural formula	NMR
89		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.82 (2H, m), 1.03-1.14 (2H, m), 1.70-1.84 (1H, m), 1.85-2.25 (12H, m), 2.25-2.42 (1H, m), 2.75-2.95 (1H, m), 3.18-4.21 (9H, m), 4.54-4.78 (2H, m), 4.87-4.97 (1H, m), 7.32-7.71 (5H, m)
90		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.85 (2H, m), 1.02-1.16 (2H, m), 1.70-1.86 (1H, m), 1.89-2.45 (6H, m), 2.83-2.96 (1H, m), 2.96-3.03 (3H, m), 3.16-3.31 (1H, m), 3.41-3.50 (0.6H, m), 3.56-4.12 (7.4H, m), 4.57-4.77 (2H, m), 5.35-5.44 (1H, m), 7.32-7.40 (1H, m), 7.41-7.61 (3H, m), 7.62-7.71 (1H, m)
91		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.81 (2H, m), 1.04-1.12 (2H, m), 1.62-2.44 (11H, m), 2.09 (3H, brs), 2.66-2.82 (3H, m), 3.05-3.17 (1H, m), 3.18-3.31 (1H, m), 3.39-3.50 (1H, m), 3.55-3.99 (5H, m), 4.00-4.15 (1H, m), 4.51-4.70 (2H, m), 4.71-4.84 (1H, m), 7.31-7.70 (5H, m)
92		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.59-0.72 (2H, m), 0.93-1.05 (2H, m), 1.67-2.02 (11H, m), 2.04-2.16 (1H, m), 2.18-2.34 (1H, m), 2.66-2.75 (3H, brs), 2.86-3.01 (2H, m), 3.09-3.32 (1H, m), 3.36-3.91 (6H, m), 3.99-4.16 (1H, m), 4.44-4.58 (2H, m), 4.63-4.80 (1H, m), 7.43-7.76 (5H, m), 10.21-10.33 (1H, m)

Table 1-24

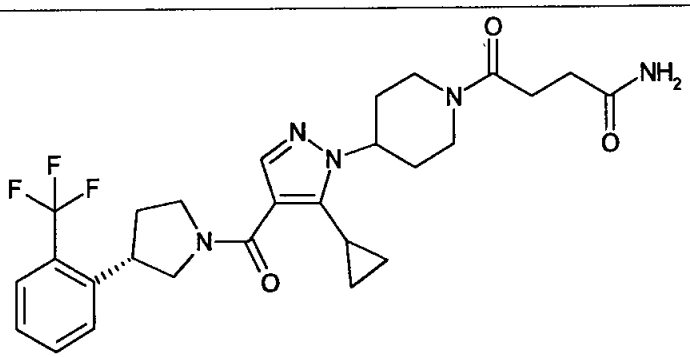
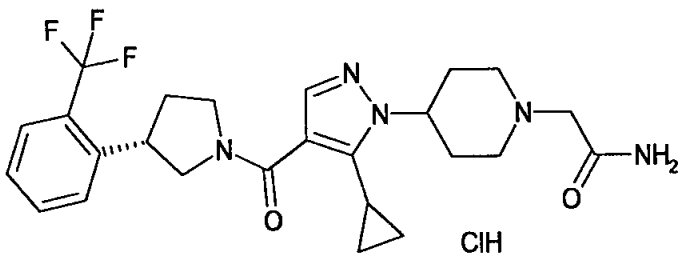
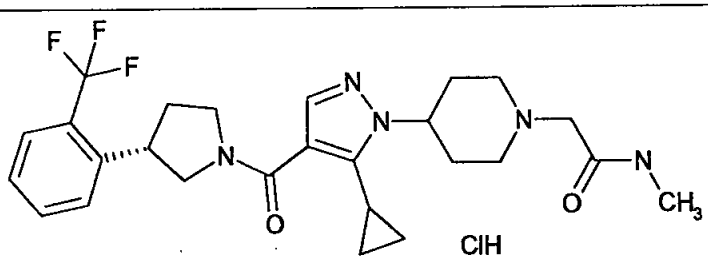
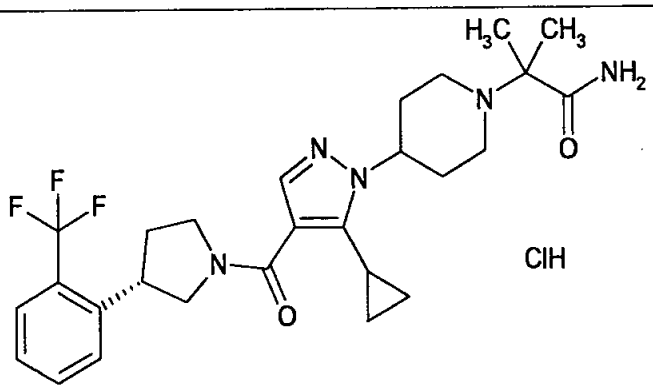
Ex. No.	structural formula	NMR
93		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.84 (2H, m), 1.03-1.12 (2H, m), 1.14-1.22 (7H, m), 1.66-2.24 (6H, m), 2.27-2.54 (2H, m), 2.79-2.96 (1H, m), 3.13-3.27 (1H, m), 3.39-3.50 (1H, m), 3.55-4.18 (6H, m), 4.53-4.79 (2H, m), 6.58-6.61 (1H, m), 7.31-7.71 (5H, m)
94		^{1}H-NMR (400MHz, DMSO-d_6) δ: 0.57-0.73 (2H, m), 0.90-1.05 (2H, m), 1.82-2.53 (8H, m), 3.23-3.79 (6H, m), 3.81-4.24 (4H, m), 4.63-4.97 (1H, m), 7.39-7.77 (6H, m), 7.98-8.17 (1H, m), 9.99-10.27 (1H, m)
95		^{1}H-NMR (400MHz, DMSO-d_6) δ: 0.59-0.75 (2H, m), 0.91-1.07 (2H, m), 1.82-2.46 (8H, m), 2.64-2.76 (3H, m), 3.21-3.99 (10H, m), 4.61-4.82 (1H, m), 7.41-7.79 (5H, m), 8.48-8.69 (1H, m), 9.99-10.24 (1H, m)
96		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.61-0.82 (2H, m), 1.02-1.18 (2H, m), 1.69 (6H, s), 1.70-1.84 (1H, m), 2.05-2.23 (3H, m), 2.29-2.46 (1H, m), 3.03-4.07 (11H, m), 5.02 (1H, brs), 5.74 (1H, brs), 7.34-7.41 (1H, m), 7.44-7.50 (1H, m), 7.51-7.60 (2H, m), 7.65-7.70 (1H, m), 9.13 (1H, brs), 11.80 (1H, brs)

Table 1-25

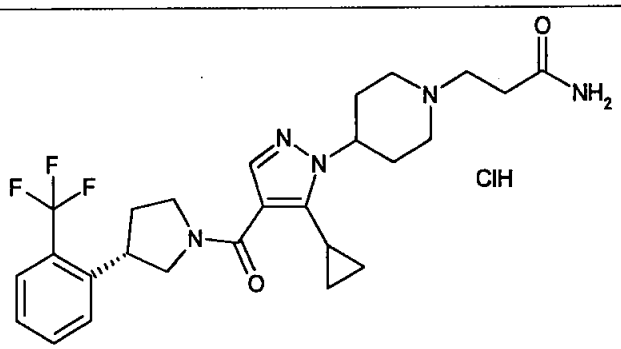
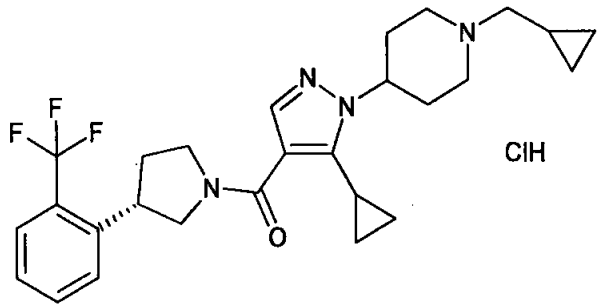
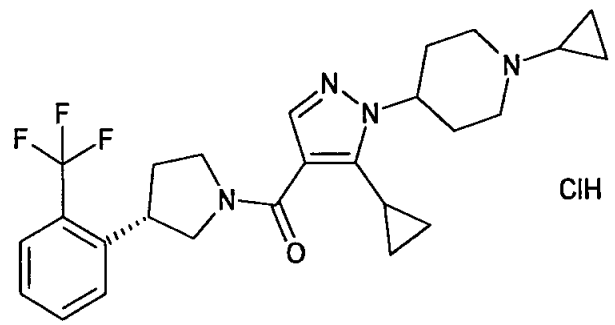
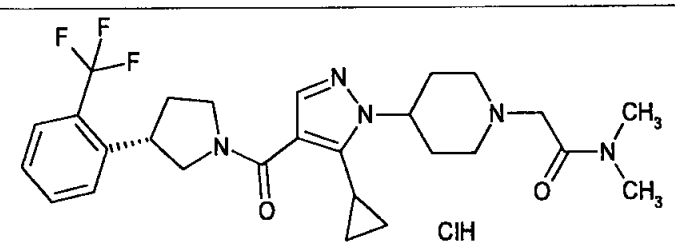
Ex. No.	structural formula	NMR
97		^{1}H-NMR (400MHz, DMSO-d_6) δ: 0.58-0.77 (2H, m), 0.90-1.06 (2H, m), 1.83-1.98 (1H, m), 2.04-2.74 (6H, m), 3.07-3.96 (13H, m), 4.64-4.97 (1H, m), 7.20-7.85 (7H, m), 10.09-10.49 (1H, m)
98		^{1}H-NMR (400MHz, DMSO-d_6) δ: 0.30-0.49 (2H, m), 0.56-0.76 (4H, m), 0.88-1.05 (2H, m), 1.07-1.22 (1H, m), 1.81-1.98 (1H, m), 1.99-2.38 (6H, m), 2.88-3.04 (2H, m), 3.09-3.26 (2H, m), 3.41-3.95 (7H, m), 4.58-4.86 (1H, m), 7.34-7.85 (5H, m), 10.17-10.53 (1H, m)
99		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.74 (2H, m), 0.75-0.85 (2H, m), 0.93-1.04 (2H, m), 1.12-1.23 (2H, m), 1.86-2.54 (7H, m), 2.71-2.82 (1H, m), 3.28-3.92 (9H, m), 4.66-4.83 (1H, m), 7.42-7.77 (5H, m), 10.60-10.79 (1H, m)
100		^{1}H-NMR (400MHz, DMSO-d_6) δ: 0.57-0.75 (2H, m), 0.91-1.05 (2H, m), 1.82-2.53 (7H, m), 2.85-3.01 (6H, m), 3.18-4.44 (11H, m), 4.62-4.83 (1H, m), 7.41-7.78 (5H, m), 9.66-9.97 (1H, br)

Table 1-26

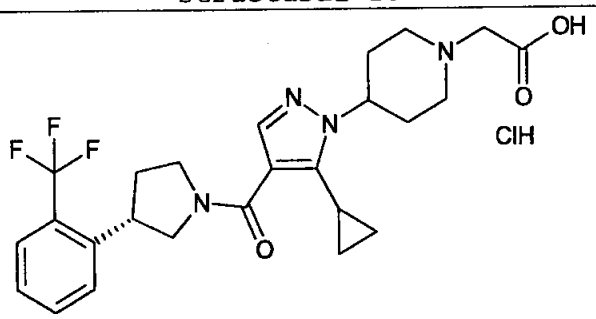
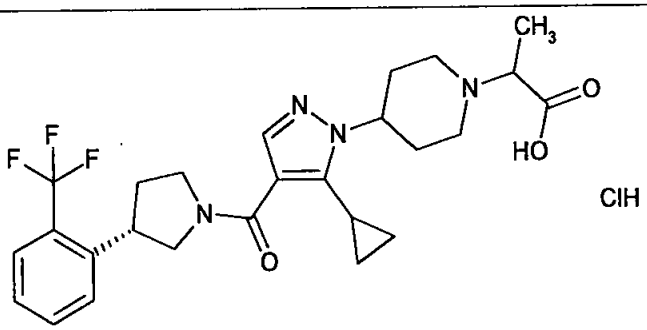
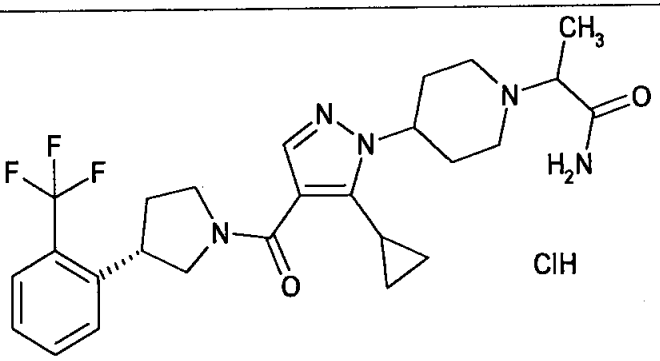
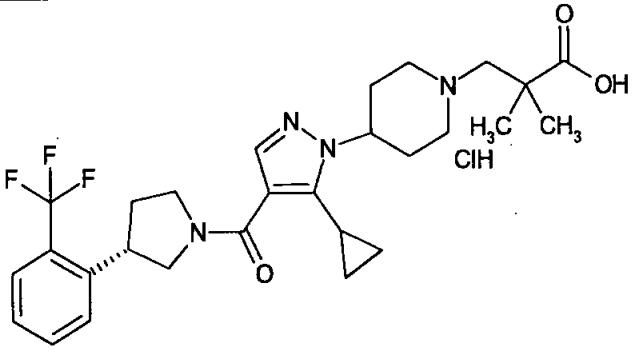
Ex. No.	structural formula	NMR
101		^{1}H-NMR (400MHz, DMSO-d_6) δ: 0.59-0.75 (2H, m), 0.91-1.06 (2H, m), 1.84-2.00 (1H, m), 2.03-2.45 (6H, m), 3.15-3.95 (9H, m), 4.06-4.23 (2H, m), 4.63-4.83 (1H, m), 7.41-7.80 (5H, m)
102		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.59-0.75 (2H, m), 0.91-1.06 (2H, m), 1.46-1.62 (4H, m), 1.84-2.60 (7H, m), 3.23-3.94 (7H,m), 4.16-4.32 (1H, m), 4.51-5.06 (2H, m), 7.40-7.79 (6H, m), 10.11-10.42 (1H, brs)
103		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.73 (2H, m), 0.92-1.04 (2H, m), 1.43-1.54 (3H, m), 2.00-2.58 (8H, m), 3.14-4.17 (9H, m), 4.68-4.85 (1H, m), 7.42-7.79 (6H, m), 8.08-8.20 (1H, m), 10.09 (1H, brs)
104		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.61-0.75 (2H, m), 0.94-1.06 (2H, m), 1.22-1.38 (6H, m), 1.82-2.62 (7H, m), 3.13-3.96 (11H, m), 4.69-4.95 (1H, m), 7.38-7.82 (6H, m), 9.23-9.88 (1H, m)

Table 1-27

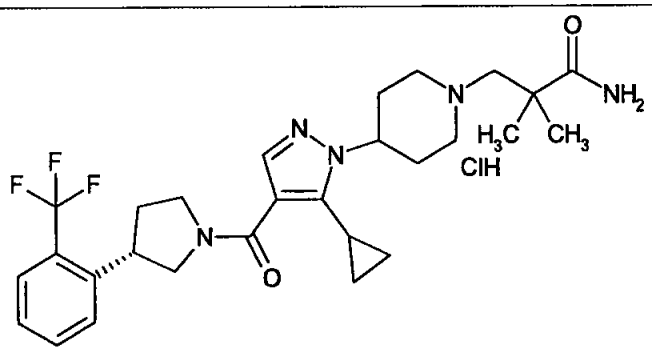
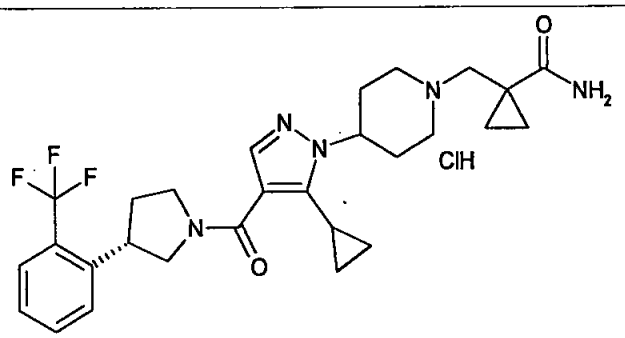
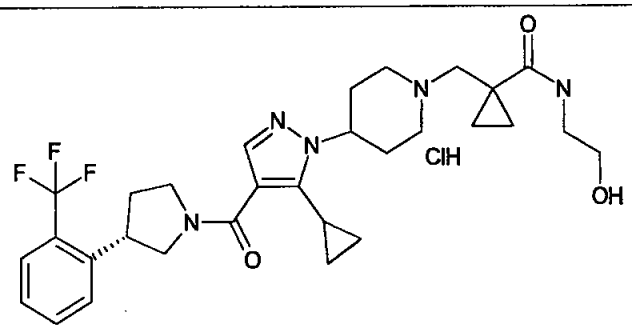
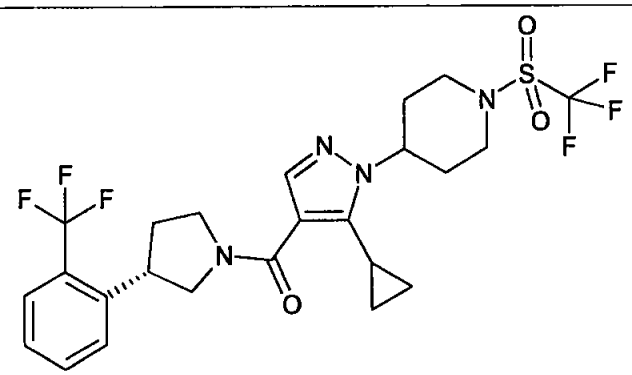
Ex. No.	structural formula	NMR
105		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.59-0.75 (2H, m), 0.93-1.06 (2H, m), 1.22-1.38 (6H, m), 1.83-1.98 (1H, m), 1.99-2.62 (6H, m), 3.14-3.94 (11H, m), 4.69-4.93 (1H, m), 7.27-7.80 (7H, m), 9.05-9.52 (1H, m)
106		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.56-0.77 (2H, m), 0.91-1.07 (2H, m), 1.15-1.39 (4H, m), 1.82-2.62 (7H, m), 3.13-4.03 (11H, m), 4.63-4.97 (1H, m), 7.06-7.32 (2H, m), 7.40-7.81 (5H, m), 9.76-10.08 (1H, m)
107		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.61-0.74 (2H, m), 0.93-1.04 (2H, m), 1.13-1.21 (2H, m), 1.25-1.34 (2H, m), 1.85-1.98 (1H, m), 2.01-2.54 (6H, m), 3.08-3.92 (16H, m), 4.64-4.84 (1H, m), 7.43-7.78 (6H, m), 9.57-9.92 (1H, m)
108		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.82 (2H, m), 1.01-1.14 (2H, m), 1.66-1.83 (1H, m), 1.94-2.44 (6H, m), 3.18-3.49 (2H, m), 3.54-4.20 (7H, m), 4.53-4.70 (1H, m), 7.28-7.72 (5H, m)

Table 1-28

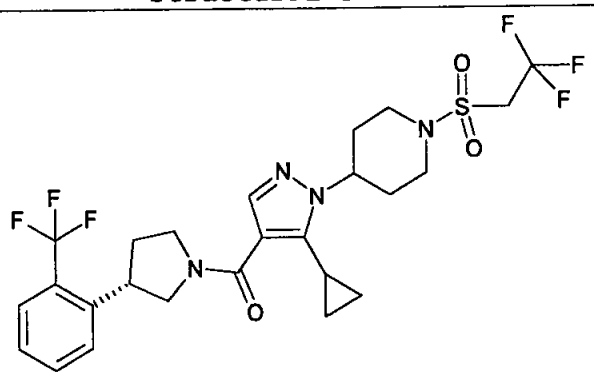
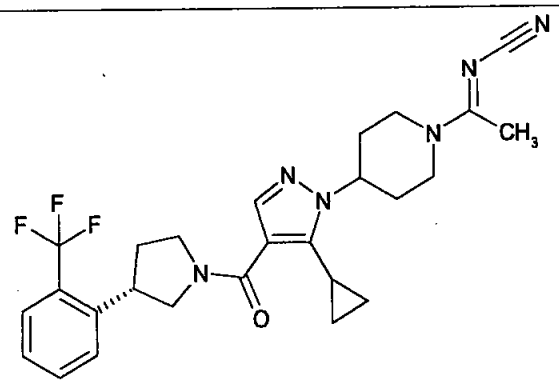
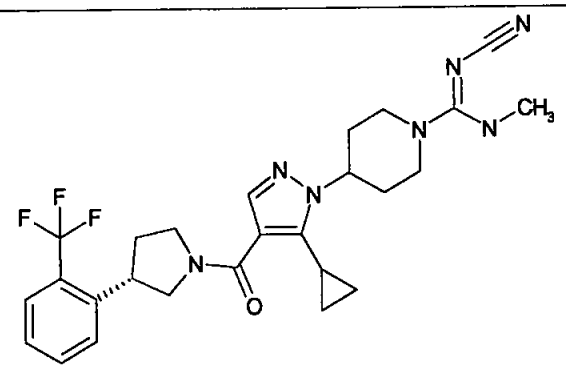
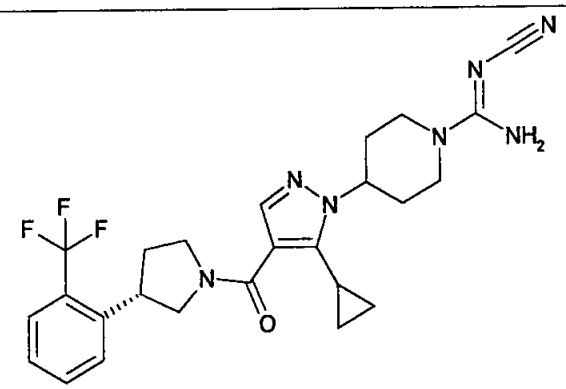
Ex. No.	structural formula	NMR
109		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.83 (2H, m), 0.99-1.11 (2H, m), 1.68-1.83 (1H, m), 1.91-2.45 (6H, m), 3.04-3.20 (2H, m), 3.38-4.11 (9H, m), 4.47-4.66 (1H, m), 7.72-8.35 (5H, m)
110		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.88 (2H, m), 0.98-1.21 (2H, m), 1.66-1.88 (1H, m), 1.89-2.54 (9H, m), 2.94-3.17 (1H, m), 3.26-3.53 (1.5H, m), 3.54-4.21 (5.5H, m), 4.58-4.93 (2H, m), 7.29-7.75 (5H, m)
111		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.62-0.83 (2H, m), 0.97-1.17 (2H, m), 1.63-1.95 (3H, m), 1.96-2.24 (3H, m), 2.25-2.47 (1H, m), 2.97-3.19 (5H, m), 3.40-3.49 (0.5H, m), 3.55-4.26 (6.5H, m), 4.46-4.69 (1H, m), 5.54-5.76 (1H, m), 7.30-7.60 (4H, m), 7.61-7.73 (1H, m)
112		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.60-0.81 (2H, m), 0.98-1.16 (2H, m), 1.62-1.82 (3H, m), 1.93-2.25 (3H, m), 2.26-2.47 (1H, m), 2.90-3.08 (2H, m), 3.35-3.50 (0.5H, m), 3.53-4.09 (4.5H, m), 4.17-4.34 (2H, m), 4.45-4.65 (1H, m), 5.94-6.14 (2H, m), 7.29-7.61 (4H, m), 7.62-7.74 (1H, m)

Table 1-29

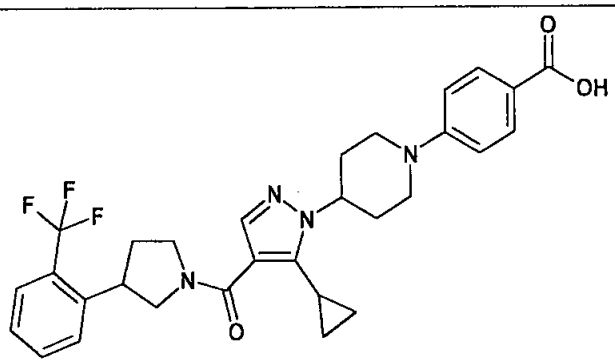
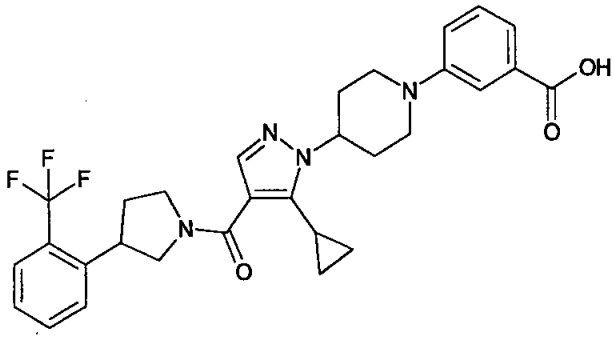
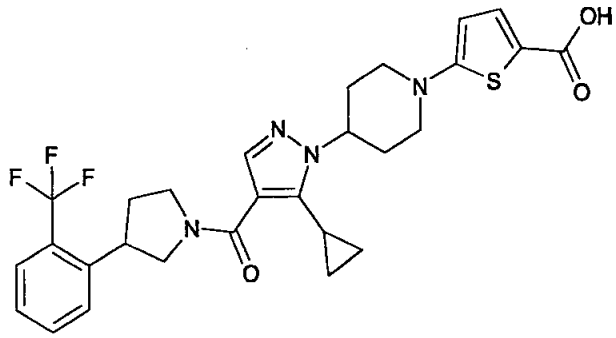
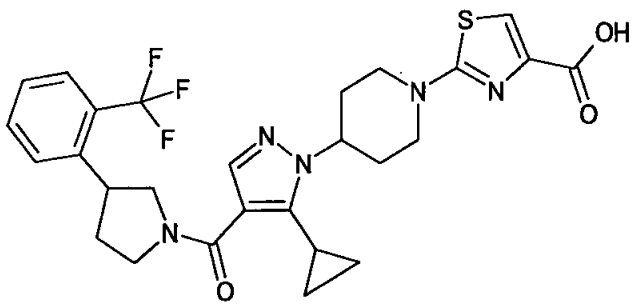
Ex. No.	structural formula	NMR
113		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.87 (2H, m), 1.03-1.18 (2H, m), 1.71-2.47 (7H, m), 3.00-3.18 (2H, m), 3.42-4.17 (7H, m), 4.56-4.75 (1H, m), 6.85-6.97 (2H, m), 7.32-7.71 (5H, m), 7.92-8.00 (2H, m)
114		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.87 (2H, m), 1.02-1.19 (2H, m), 1.74-2.50 (7H, m), 2.81-3.19 (2H, m), 3.44-4.14 (7H, m), 4.48-4.80 (1H, m), 7.07-7.85 (9H, m)
115		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.59-0.77 (2H, m), 0.92-1.08 (2H, m), 1.87-2.36 (7H, m), 3.08-3.94 (9H, m), 4.60-4.81 (1H, m), 6.16-6.29 (1H, m), 7.38-7.80 (6H, m), 12.25(1H, bs)
116		^{1}H-NMR (300MHz, DMSO-D6) δ: 0.62-0.73 (2H, m), 0.96-1.04 (2H, m), 1.87-2.33 (7H, m), 3.18-3.32 (3H, m), 3.44-3.91 (4H, m), 3.97-4.10 (2H, m), 4.66-4.80 (1H, m), 7.41-7.60 (2H, m), 7.63-7.78 (4H, m), 12.6 (1H, brs)

Table 1-30

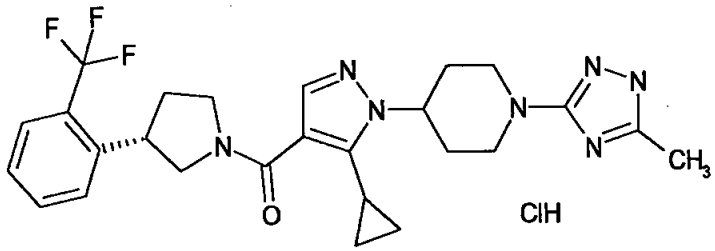
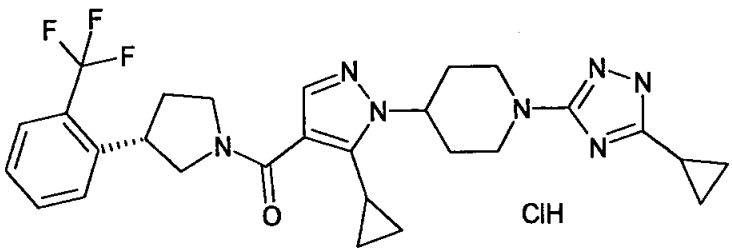
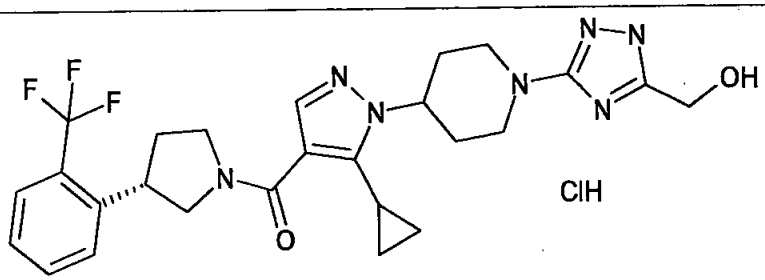
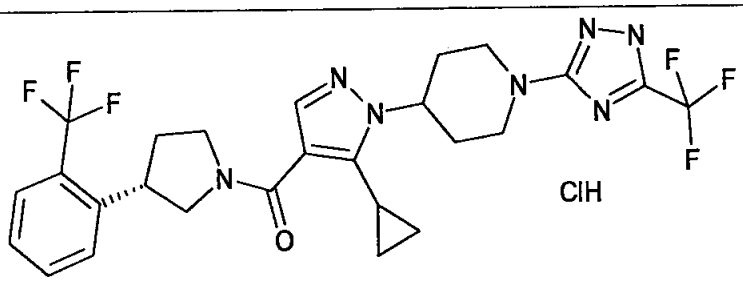
Ex. No.	structural formula	NMR
117		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.59-0.77 (2H, m), 0.93-1.08(2H, m), 1.88-2.39 (10H, m), 3.21-4.12 (11H, m), 4.64-4.84 (1H, m), 7.41-7.80 (5H, m)
118		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.60-0.75 (2H, m), 0.89-1.09 (6H, m), 1.86-2.36 (8H, m), 3.11-4.11 (11H, m), 4.61-4.82 (1H, m), 7.41-7.80 (5H, m)
119		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.60-0.76 (2H, m), 0.92-1.06 (2H, m), 1.88-2.38 (8H, m), 3.15-4.15 (10H, m), 4.42-4.53 (2H, m), 4.63-4.82 (1H, m), 7.39-7.79 (6H, m)
120		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.58-0.77 (2H, m), 0.92-1.06 (2H, m), 1.85-2.41 (7H, m), 3.11-4.10 (9H, m), 4.31-5.07 (2H, m), 7.41-7.79 (5H, m), 13.3-13.5 (1H, m)

Table 1-31

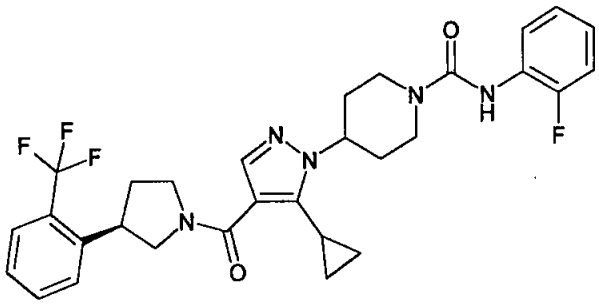
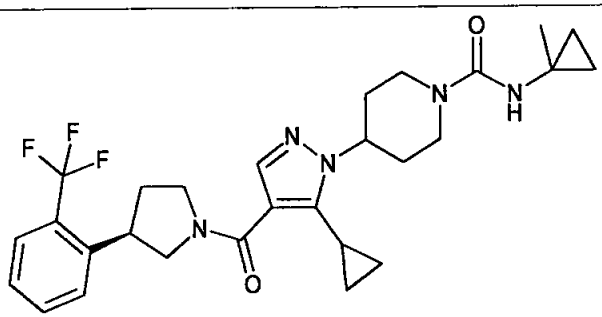
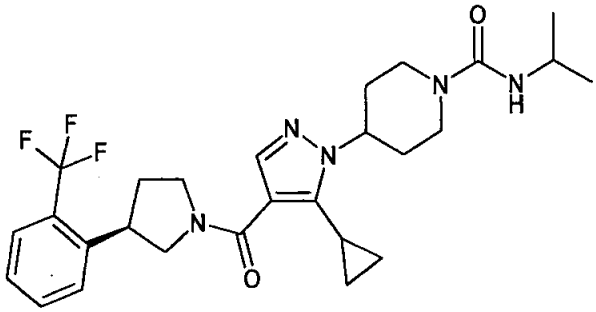
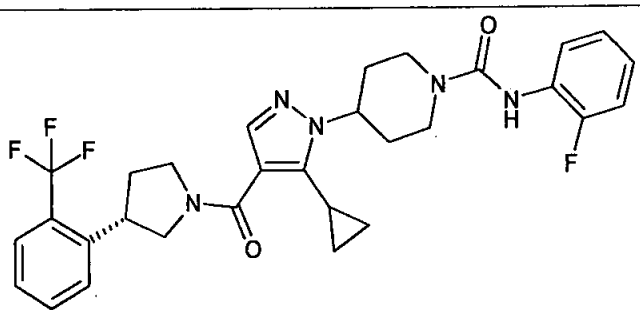
Ex. No.	structural formula	NMR
121		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.72-0.87 (2H, m), 1.05-1.15 (2H, m), 1.49-2.48 (7H, m), 3.05-3.22 (2H, m), 3.40-4.14 (5H, m), 4.20-4.36 (2H, m), 4.52-4.73 (1H, m), 6.60-6.71 (1H, m), 6.94-7.16 (3H, m), 7.33-7.72 (5H, m), 8.04-8.14 1H, m)
122		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.57-0.66 (2H, m), 0.66-0.84 (4H, m), 1.01-1.13 (2H, m), 1.32-1.45 (3H, m), 1.55-2.48 (7H, m), 2.81-3.00 (2H, m), 3.41-4.15 (5H, m), 4.44-4.63 (2H, m), 4.85-4.96 (1H, m), 7.33-7.71 (6H, m)
123		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.82 (2H, m), 1.02-1.13 (2H, m), 1.13-1.22 (6H, m),1.55-2.47 (8H, m), 2.84-3.01 (2H, m), 3.41-4.34 (9H, m), 4.45-4.63 (1H, m), 7.30-7.71 (6H, m)
124		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.72-0.87 (2H, m), 1.04-1.17 (2H, m), 1.53-2.46 (7H, m), 3.05-3.21 (2H, m), 3.42-4.11 (5H, m), 4.20-4.35 (2H, m), 4.55-4.71 (1H, m), 6.62-6.70 (1H, m), 6.93-7.16 (3H, m), 7.33-7.72 (5H, m), 8.04-8.14 (1H, m)

Table 1-32

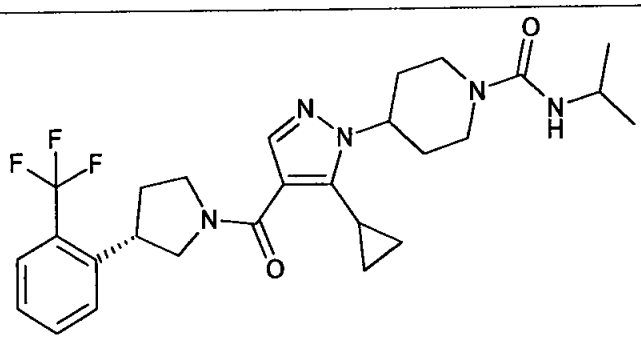
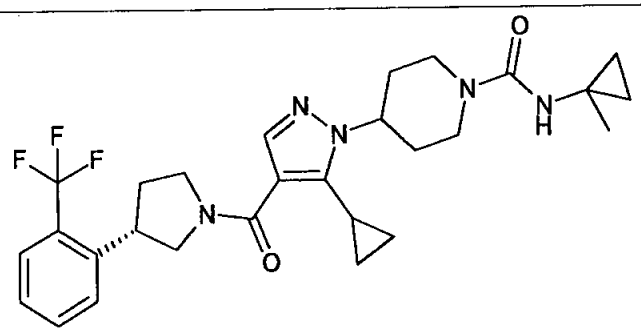
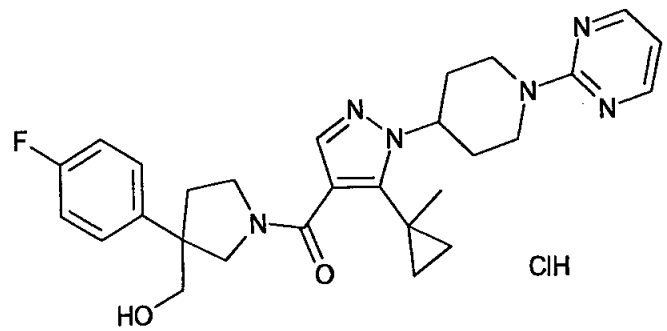
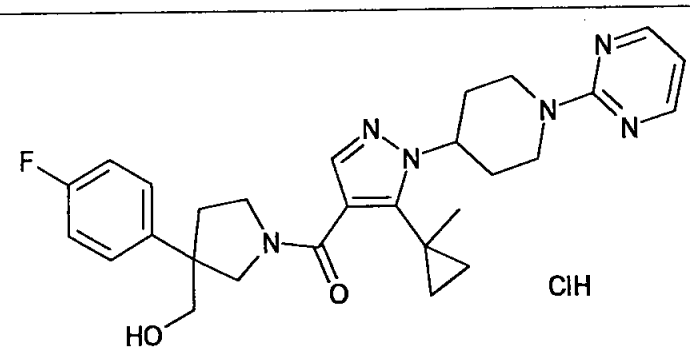
Ex. No.	structural formula	NMR
125		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.84 (2H, m), 1.03-1.13 (2H, m), 1.13-1.21 (6H, m), 1.55-2.47 (8H, m), 2.84-3.01 (2H, m), 3.41-4.31 (9H, m), 4.45-4.63 (1H, m), 7.33-7.72 (6H, m)
126		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.58-0.66 (2H, m), 0.66-0.83 (4H, m), 1.02-1.11 (2H, m), 1.36-1.43 (3H, m), 1.53-2.46 (7H, m), 2.83-2.99 (2H, m), 3.41-4.15 (5H, m), 4.45-4.61 (2H, m), 4.85-4.92 (1H, m), 7.32-7.72 (6H, m)
127		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.56-0.86 (4H, m), 1.32-1.43 (3H, m), 1.85-2.12 (6H, m), 2.28-2.39 (1H, m), 3.09-3.26 (2H, m), 3.31-4.94 (6H, m), 4.74-4.91 (3H, m), 6.30 (1H, bs), 6.69-6.75 (1H, m), 7.07-7.37 (4H, m), 7.53-7.62 (1H, m), 8.40-8.50 (2H, m)
128		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.56-0.88 (4H, m), 1.32-1.48 (3H, m), 1.85-2.12 (6H, m), 2.28-2.39 (1H, m), 3.09-3.24 (2H, m), 3.30-4.95 (6H, m), 4.73-4.93 (3H, m), 5.81 (1H, bs), 6.64-6.73 (1H, m), 7.06-7.40 (4H, m), 7.50-7.67 (1H, m), 8.39-8.49 (2H, m)

Table 1-33

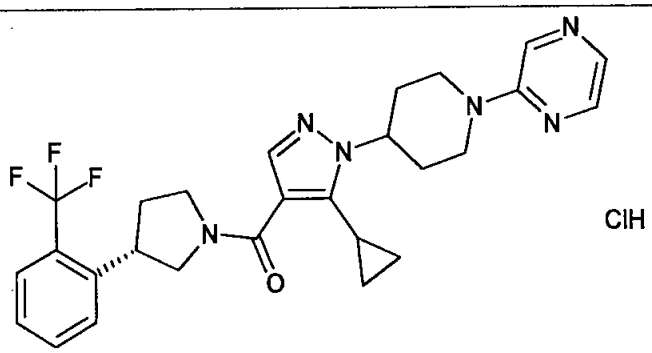
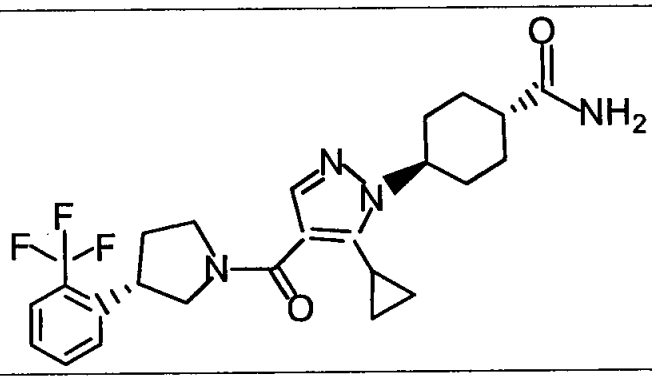
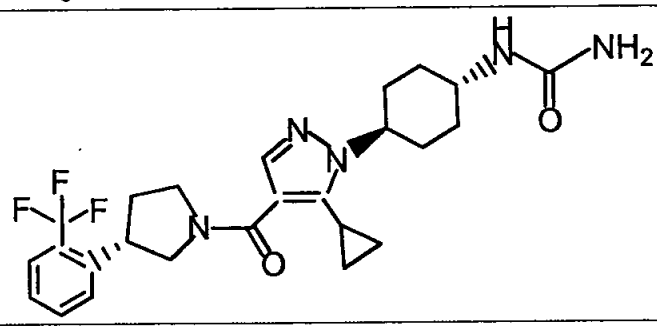
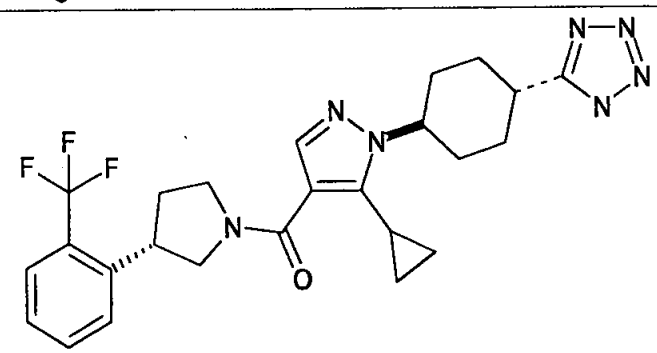
Ex. No.	structural formula	NMR
129		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.66-0.69 (2H, m), 0.99-1.01 (2H, m), 1.91-2.33 (7H, m), 3.11-3.14 (2H, m), 3.46-3.89 (5H, m), 4.49-4.52 (2H, m), 4.75-4.77 (1H, m), 7.48-7.74 (6H, m), 7.85-7.90 (1H, m), 8.17 (1H, brs), 8.43-8.45 (1H, m)
130		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.79 (2H, m), 0.94-1.10 (2H, m), 1.63-2.44 (12H, m), 3.38-4.10 (5H, m), 4.32-4.51 (1H, m), 5.33 (1H, br), 5.51 (1H, br), 7.27-7.70 (5H, m)
131		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.62-0.82 (2H, m), 0.95-1.10 (2H, m), 1.23-1.39 (2H, m), 1.65-2.45 (8H, m), 3.40-4.10 (6H, m), 4.26-4.60 (4H, m), 7.27-7.71 (6H, m)
132		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.79 (2H, m), 0.84-0.92 (2H, m), 1.06-1.15 (2H, m), 1.22-1.35 (3H, m), 1.73-2.49 (8H, m), 3.05-3.19 (1H, m), 3.39-3.55 (1H, m), 3.61-4.17 (3H, m), 4.46-4.61 (1H, m), 7.33-7.71 (5H, m)

Table 1-34

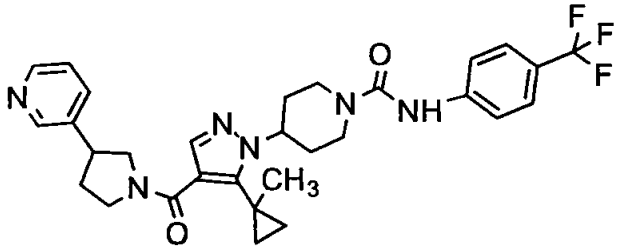
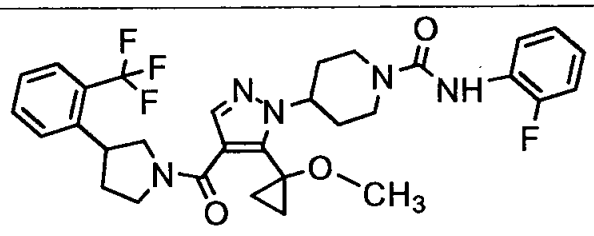
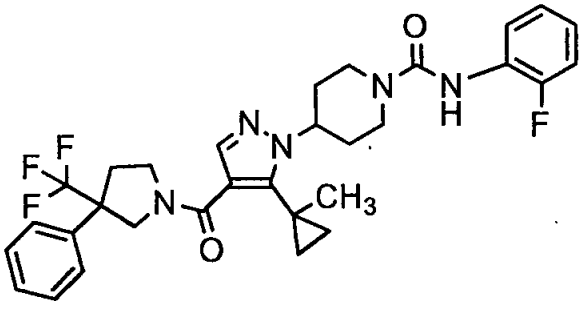
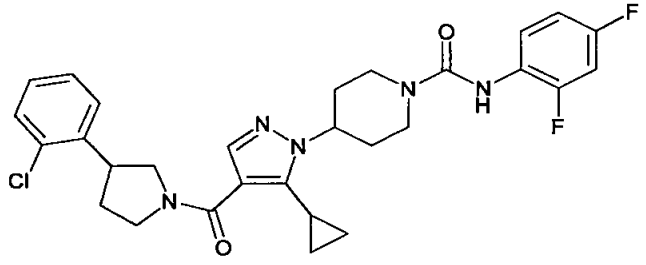
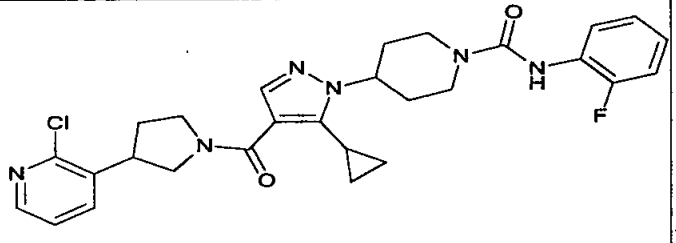
Ex. No.	structural formula	NMR
133		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.95 (4H, m), 1.38-1.47 (3H, m), 1.61-1.88 (2H, m), 1.99-2.29 (3H, m), 2.34-2.50 (1H, m), 2.94-3.12 (2H, m), 3.36-4.18 (5H, m), 4.25-4.40 (2H, m), 4.54-4.72 (1H, m), 6.99-7.33 (2H, m), 7.44-7.65 (6H, m), 8.44-8.61 (2H, m)
134		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.89-1.05 (2H, m), 1.22-1.34 (2H, m), 1.94-2.44 (6H, m), 3.05-3.21 (2H, m), 3.28-3.39 (3H, m), 3.42-4.11 (5H, m), 4.20-4.35 (2H, m), 4.77-4.93 (1H, m), 6.62-6.71 (1H, m), 6.93-7.18 (3H, m), 7.32-7.72 (5H, m), 8.05-8.14 (1H, m)
135		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.57-0.95 (4H, m), 1.34-1.54 (3H, m), 1.83-2.08 (2H, m), 2.18-2.41 (2H, m), 2.45-2.61 (1H, m), 2.73-2.92 (1H, m), 3.02-3.24 (2H, m), 3.51-4.86 (7H, m), 6.60-6.78 (1H, m), 6.93-7.18 (3H, m), 7.20-7.46 (5H, m), 7.46-7.57 (1H, m), 8.01-8.15 (1H, m)
136		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.81 (2H, m), 1.00-1.14 (2H, m), 1.71-1.85 (1H, m), 1.93-2.43 (6H, m), 3.05-3.19 (2H, m), 3.40-4.10 (5H, m), 4.20-4.33 (2H, m), 4.55-4.69 (1H, m), 6.48-6.57 (1H, m), 6.81-6.92 (2H, m), 7.17-7.45 (4H, m), 7.50-7.60 (1H, m), 7.94-8.03 (1H, m)
137		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.83 (2H, m), 1.01-1.14 (2H, m), 1.75-1.86 (1H, m), 1.94-2.36 (6H, m), 2.37-2.49 (1H, m), 3.07-3.20 (2H, m), 3.40-4.14 (4H, m), 4.22-4.34 (2H, m), 4.57-4.71 (1H, m), 6.61-6.70 (1H, m), 6.93-7.03 (1H, m), 7.03-7.17 (3H, m), 7.51-7.70 (2H, m), 8.02-8.15 (1H, m), 8.28-8.37 (1H, brs)

Table 1-35

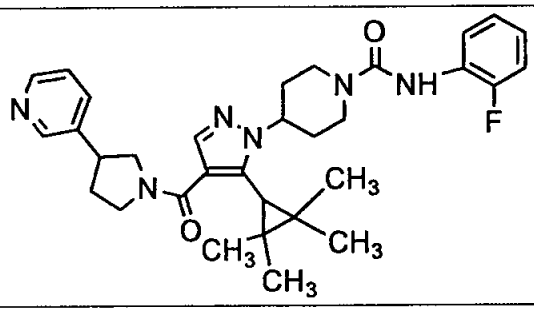
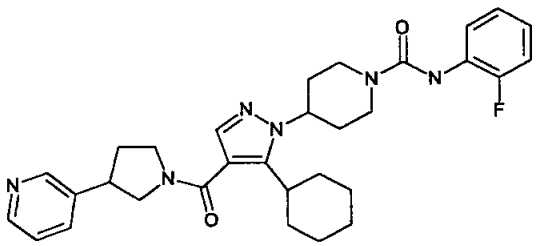
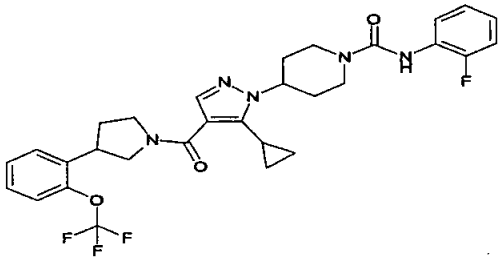
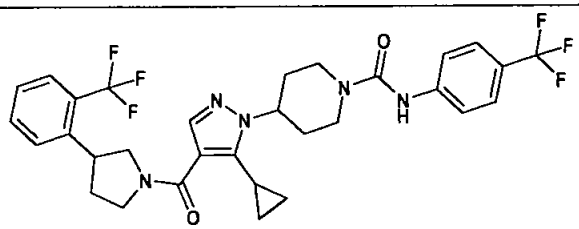
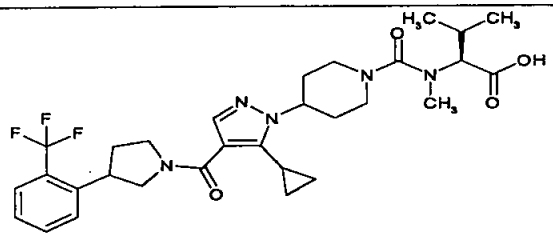
Ex. No.	structural formula	NMR
138		^{1}H-NMR ($CDCl_3$) δ: 0.94 (6H, s), 1.33 (6H, s), 2.03-2.11 (4H, m), 2.36-2.39 (2H, m), 3.07-3.09 (2H, m), 3.37-3.76 (4H, m), 3.89-3.96 (1H, m), 4.28-4.32 (4H, m), 6.65 (1H, s), 7.01-7.08 (3H, m), 7.24-7.32 (1H, m), 7.53-7.63 (2H, m), 8.07-8.09 (1H, m), 8.53-8.57 (2H, m)
139		^{1}H-NMR (300MHz, $CDCl_3$) δ: 1.25-1.48 (3H, m), 1.69-2.48 (13H, m), 2.85-3.19 (3H, m), 3.33-4.41 (8H, m), 6.59-6.69 (1H, m), 6.89-7.14 (3H, m), 7.23-7.36 (1H, m), 7.43-7.68 (2H, m), 8.05 (1H, t, J = 8.1 Hz), 8.44-8.59 (2H, m)
140		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.83 (2H, m), 1.01-1.15 (2H, m), 1.72-1.86 (1H, m), 1.92-2.43 (6H, m), 3.03-3.20 (2H, m), 3.36-4.11 (5H, m), 4.20-4.34 (2H, m), 4.55-4.71 (1H, m), 6.66 (1H, br s), 6.93-7.16 (3H, m), 7.20-7.42 (4H, m), 7.48-7.63 (1H, m), 8.03-8.14 (1H, m)
141		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.66-0.80 (2H, m), 1.00-1.12 (2H, m), 1.58-1.82 (3H, m), 1.97-2.23 (3H, m), 2.27-2.47 (1H, m), 2.90-3.06 (2H, m), 3.40-4.11 (5H, m), 4.24-4.41 (2H, m), 4.46-4.62 (1H, m), 7.32-7.73 (10H, m)
142		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.57-0.74 (2H, m), 0.81-1.03 (8H, m), 1.79-2.36 (8H, m), 2.82-2.90 (8H, m), 3.44-3.92 (9H, m), 4.50-4.70 (1H, s), 7.42-7.53 (2H, m), 7.55-7.61 (1H, m), 7.66-7.78 (2H, m)

Table 1-36

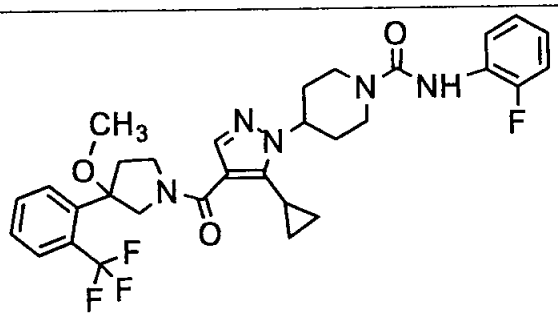
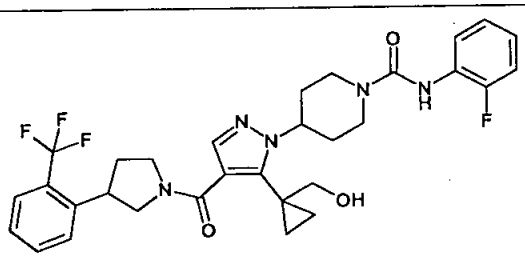
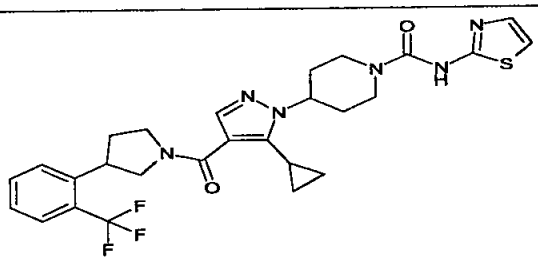
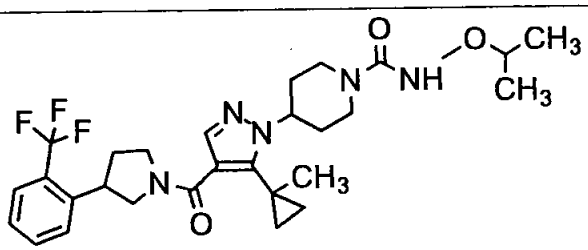
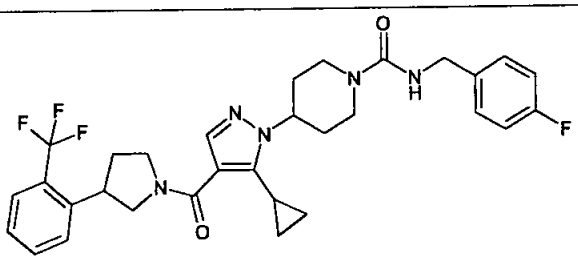
Ex. No.	structural formula	NMR
143		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.62-0.84 (2H, m), 0.91-1.17 (2H, m), 1.67-1.88 (1H, m), 1.91-2.08 (2H, m), 2.14-2.42 (2.5H, m), 2.43-2.56 (0.5H, m), 2.57-2.72 (1H, m), 2.88-3.21 (5H, m), 3.45-3.61 (0.6H, m), 3.64-3.91 (2H, m), 3.98-4.13 (1H, m), 4.19-4.36 (2.4H, m), 4.53-4.72 (1H, m), 6.63-6.79 (1H, m), 6.89-7.18 (3H, m), 7.40-7.64 (4H, m), 7.75-7.93 (1H, m), 8.00-8.13 (1H, m)
144		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.97 (2H, m), 0.97-1.35 (2H, m), 1.85-2.54 (6H, m), 2.87-3.21 (2H, m), 3.21-4.14 (7H, m), 4.16-4.46 (2H, m), 4.51-4.79 (1H, m), 5.98-6.35 (1H, m), 6.56-6.78 (1H, m), 6.85-7.20 (3H, m), 7.20-7.79 (5H, m), 7.95-8.16 (1H, m)
145		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.84 (2H, m), 1.01-1.16 (2H, m), 1.68-1.85 (1H, m), 1.88-2.46 (6H, m), 3.02-3.19 (2H, m), 3.40-4.11 (5H, m), 4.24-4.41 (2H, m), 4.53-4.71 (1H, m), 6.82-6.91 (1H, m), 7.30-7.72 (7H, m)
146		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.99 (4H, m), 1.15-1.31 (6H, m), 1.35-1.52 (3H, m), 1.73-1.98 (2H, m), 1.98-2.47 (4H, m), 2.86-3.08 (2H, m), 3.42-4.11 (6H, m), 4.12-4.31 (2H, m), 4.53-4.72 (1H, m), 7.08-7.21 (1H, m), 7.30-7.40 (1H, m), 7.41-7.61 (3H, m), 7.61-7.74 (1H, m)
147		^{1}H-NMR (300MHz, $CDCl_3$) δ: 0.64-0.81 (2H, m), 0.96-1.13 (2H, m), 1.55-1.93 (3H, m), 1.95-2.44 (4H, m), 2.84-3.02 (2H, m), 3.36-4.22 (7H, m), 4.30-4.41 (2H, m), 4.43-4.62 (1H, m), 4.83-4.99 (1H, m), 6.91-7.05 (2H, m), 7.17-7.71 (7H, m)

Table 1-37

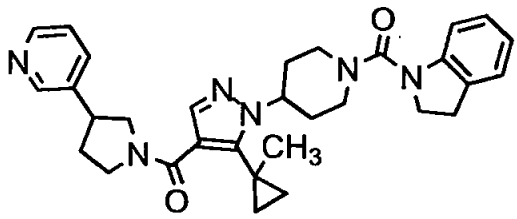
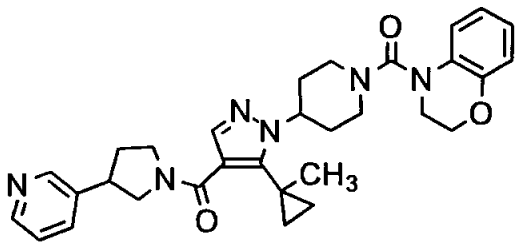
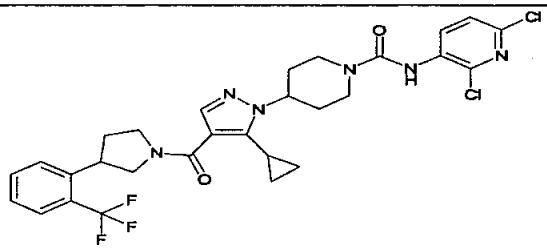
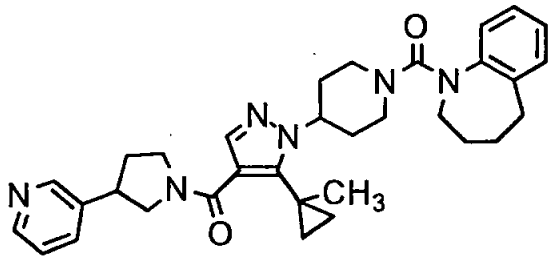
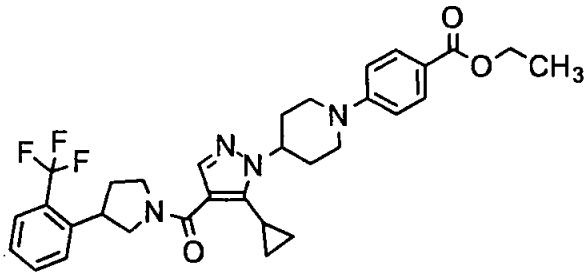
Ex. No.	structural formula	NMR
148		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.73-0.84 (2H, m), 0.85-0.96 (2H, m), 1.45 (3H, s), 1.84-1.97 (2H, m), 2.01-2.20 (1H, m), 2.26-2.49 (3H, m), 2.97-3.12 (4H, m), 3.37-4.19 (9H, m), 4.61-4.75 (1H, m), 6.86-6.95 (1H, m), 7.08-7.22 (3H, m), 7.25-7.33 (1H, m), 7.48-7.65 (2H, m), 8.46-8.63 (2H, m)
149		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.82 (2H, m), 0.82-0.96 (2H, m), 1.42 (3H, s), 1.79-1.97 (2H, m), 1.98-2.19 (4H, m), 2.93-3.08 (2H, m), 3.33-3.82 (5.5H, m), 3.84-4.01 (1H, m), 4.04-4.23 (2.5H, m), 4.26-4.40 (2H, m), 4.55-4.73 (1H, m), 6.81-6.97 (3H, m), 7.11-7.22 (1H, m), 7.23-7.35 (1H, m), 7.46-7.67 (2H, m), 8.44-8.62 (2H, m)
150		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.85 (2H, m), 1.02-1.18 (2H, m), 1.72-1.87 (1H, m), 1.94-2.46 (6H, m), 3.08-3.26 (2H, m), 3.41-4.11 (5H, m), 4.18-4.33 (2H, m), 4.57-4.75 (1H, m), 6.97-7.07 (1H, m), 7.23-7.61 (5H, m), 7.64-7.72 (1H, m), 8.53-8.60 (1H, m)
151		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.61-0.89 (4H, m), 1.36 (3H, s), 1.55-1.83 (6H, m), 1.89-2.17 (3H, m), 2.32-2.47 (1H, m), 2.59-2.82 (4H, m), 3.33-4.18 (9H, m), 4.38-4.52 (1H, m), 7.03-7.14 (2H, m), 7.16-7.32 (3H, m), 7.43-7.64 (2H, m), 8.44-8.61 (2H, m)
152		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.85 (2H, m), 1.03-1.16 (2H, m), 1.33-1.42 (3H, m), 1.73-1.88 (1H, m), 1.93-2.22 (3H, m), 2.25-2.45 (3H, m), 2.96-3.13 (2H, m), 3.41-4.11 (7H, m), 4.28-4.39 (2H, m), 4.52-4.71 (1H, m), 6.85-6.96 (2H, m), 7.32-7.40 (1H, m), 7.41-7.61 (3H, m), 7.63-7.71 (1H, m), 7.89-7.99 (2H, m)

Table 1-38

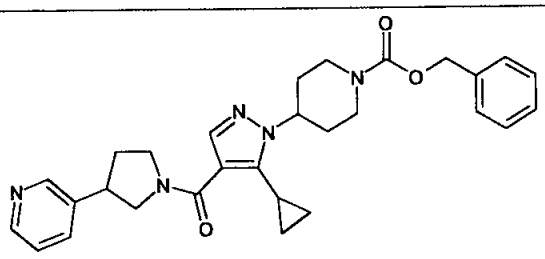
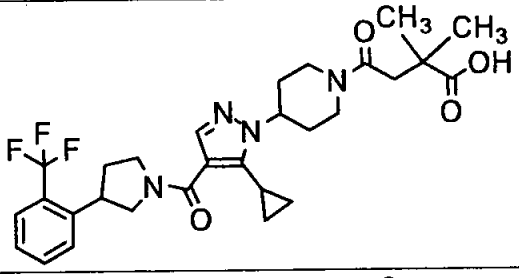
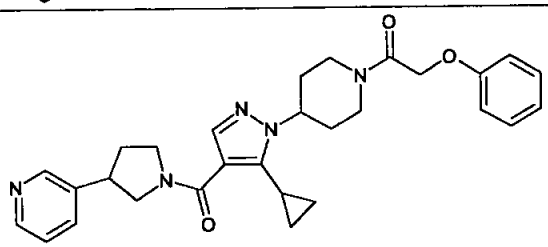
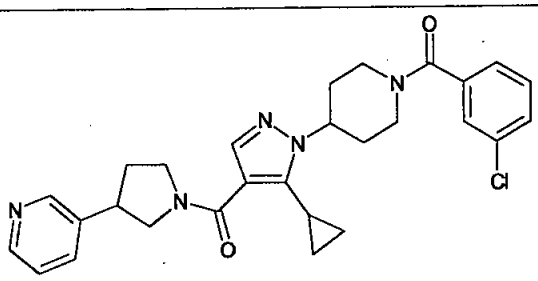
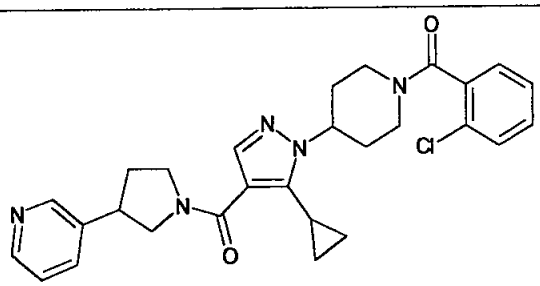
Ex. No.	structural formula	NMR
153		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.79 (2H, m), 1.00-1.09 (2H, m), 1.70-1.97 (3H, m), 2.00-2.26 (3H, m), 2.31-2.47 (1H, m), 2.86-3.05 (2H, m), 3.35-3.53 (1.5H, m), 3.56-3.77 (2H, m), 3.84-3.94 (1H, m), 4.08-4.16 (0.5H, m), 4.25-4.61 (3H, m), 5.14 (2H, s), 7.23-7.40 (6H, m), 7.49-7.61 (2H, m), 8.47-8.57 (2H, m)
154		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.61-0.86 (2H, m), 0.98-1.18 (2H, m), 1.23-1.41 (6H, m), 1.67-1.86 (1H, m), 1.87-2.47 (6H, m), 2.52-2.88 (3H, m), 3.06-3.32 (1H, m), 3.35-4.15 (6H, m), 4.49-4.85 (2H, m), 7.28-7.73 (5H, m)
155		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.62-0.83 (2H, m), 0.97-1.14 (2H, m), 1.66-2.50 (8H, m), 2.78-2.95 (1H, m), 3.16-3.34 (1H, m), 3.37-3.54 (1H, m), 3.57-3.79 (2H, m), 3.83-3.97 (1H, m), 4.09-4.29 (1H, m), 4.54-4.80 (4H, m), 6.89-7.04 (3H, m), 7.21-7.38 (3H, m), 7.48-7.68 (2H, m), 8.42-8.70 (2H, m)
156		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.82 (2H, m), 1.00-1.13 (2H, m), 1.67-2.30 (9H, m), 2.32-2.51 (1H, m), 2.72-3.34 (2H, m), 3.36-4.03 (4H, m), 4.56-4.99 (1H, m), 7.20-7.46 (5H, m), 7.49-7.65 (2H, m), 8.42-8.62 (2H, m)
157		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.85 (2H, m), 0.98-1.13 (2H, m), 1.57-1.92 (3H, m), 1.96-2.50 (5H, m), 2.90-3.54 (3H, m), 3.56-3.81 (3H, m), 3.83-3.98 (1H, m), 4.53-4.73 (1H, m), 4.85-5.04 (1H, m), 7.21-7.47 (5H, m), 7.49-7.65 (2H, m), 8.45-8.62 (2H, m)

Table 1-39

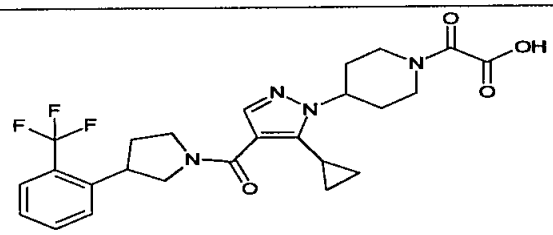
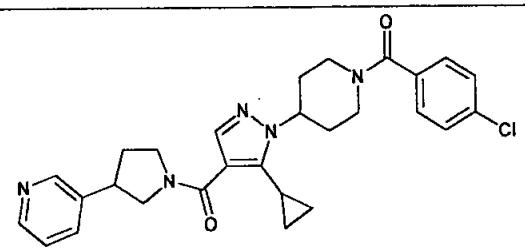
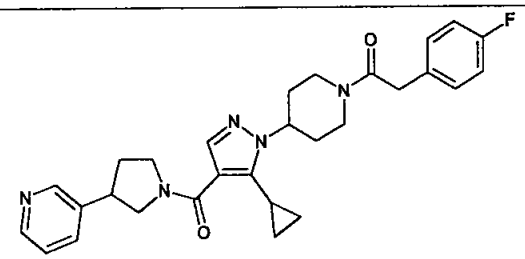
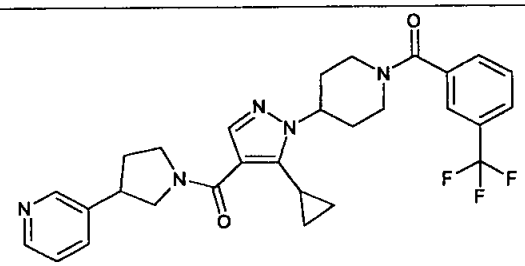
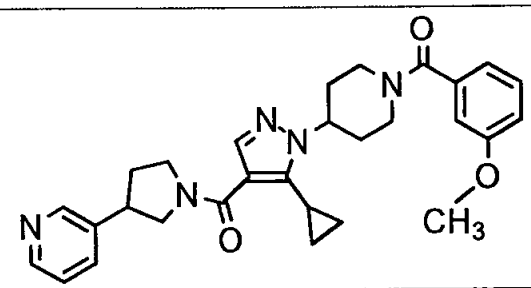
Ex. No.	structural formula	NMR
158		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.62-1.19 (4H, m), 1.62-2.53 (7H, m), 2.70-2.92 (1H, m), 3.08-3.29 (1H, m), 3.33-4.21 (6H, m), 4.51-4.75 (2H, m), 7.31-7.62 (4H, m), 7.63-7.73 (1H, m)
159		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.82 (2H, m), 0.98-1.12 (2H, m), 1.65-2.32 (9H, m), 2.34-2.50 (1H, m), 3.08 (2H, brs), 3.34-4.00 (4H, m), 4.56-4.95 (1H, m), 7.23-7.32 (1H, m), 7.35-7.44 (4H, m), 7.48-7.65 (2H, m), 8.45-8.61 (2H, m)
160		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.59-0.83 (2H, m), 0.95-1.14 (2H, m), 1.62-2.20 (6H, m), 2.30-2.50 (1H, m), 2.69-2.91 (1H, m), 3.06-3.27 (1H, m), 3.33-4.20 (6H, m), 3.73 (2H, s), 4.50-4.66 (1H, m), 4.71-4.85 (1H, m), 6.93-7.10 (2H, m), 7.15-7.34 (3H, m), 7.45-7.64 (2H, m), 8.41-8.62 (2H, m)
161		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.81 (2H, m), 0.99-1.13 (2H, m), 1.72-2.50 (9H, m), 2.85-3.33 (2H, m), 3.35-3.78 (3H, m), 3.81-4.96 (3H, m), 7.22-7.33 (1H, m), 7.47-7.77 (6H, m), 8.44-8.63 (2H, m)
162		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.82 (2H, m), 1.00-1.12 (2H, m), 1.71-2.32 (8H, m), 2.33-2.51 (1H, m), 2.85-3.28 (2H, m), 3.32-4.05 (5H, m), 3.83 (3H, s), 4.57-4.99 (1H, m), 6.90-7.04 (3H, m), 7.24-7.38 (2H, m), 7.50-7.69 (2H, m), 8.53 (2H, brs)

Table 1-40

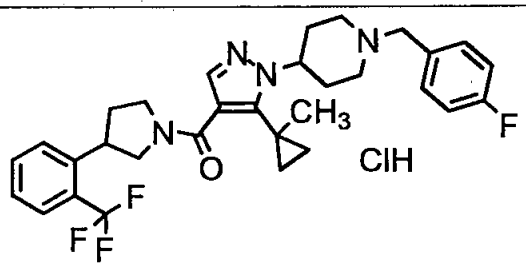
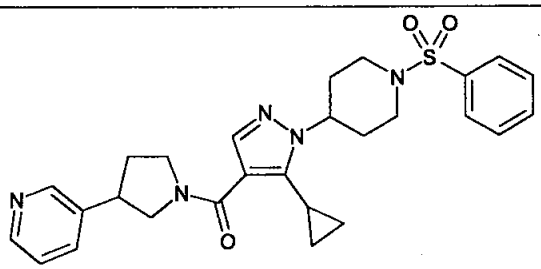
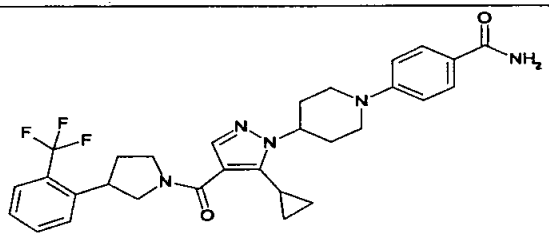
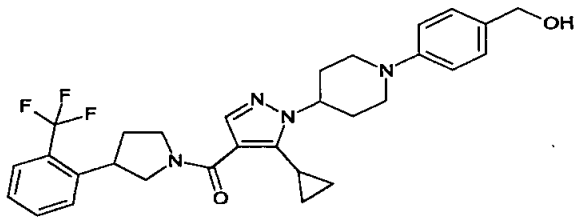
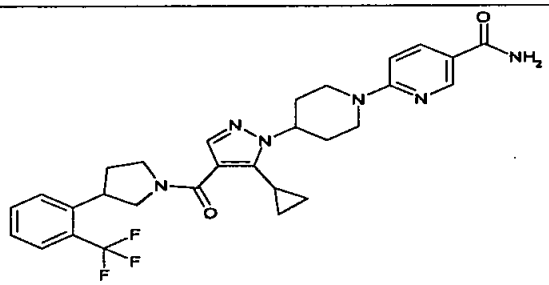
Ex. No.	structural formula	NMR
163		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.68-0.86 (4H, m), 1.29-1.38 (3H, m), 1.99-2.17 (2H, m), 2.18-2.66 (5H, m), 3.14-3.32 (2H, m), 3.39-4.50 (8H, m), 4.68-4.83 (1H, m), 7.30-7.40 (2H, m), 7.43-7.53 (1H, m), 7.60-7.82 (6H, m), 10.55-10.76 (1H, m)
164		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.59-0.74 (2H, m), 0.93-1.04 (2H, m), 1.61-1.73 (1H, m), 1.88-2.16 (3H, m), 2.25-2.59 (5H, m), 3.34-3.76 (3.5H, m), 3.83-4.01 (3H, m), 4.08-4.15 (0.5H, m), 4.27-4.39 (1H, m), 7.23-7.31 (1H, m), 7.49-7.67 (5H, m), 7.79-7.84 (2H, m), 8.46-8.58 (2H, m)
165		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.86 (2H, m), 1.00-1.19 (2H, m), 1.73-1.88 (1H, m), 1.92-2.21 (3H, m), 2.24-2.47 (3H, m), 2.92-3.12 (2H, m), 3.40-4.12 (7H, m), 4.51-4.69 (1H, m), 5.74 (2H, br s), 6.87-6.99 (2H, m), 7.31-7.40 (1H, m), 7.41-7.61 (3H, m), 7.63-7.78 (3H, m)
166		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.85 (2H, m), 1.01-1.16 (2H, m), 1.51-1.67 (1H, m), 1.75-1.89 (1H, m), 1.91-2.23 (3H, m), 2.26-2.49 (3H, m), 2.83-3.00 (2H, m), 3.40-4.12 (7H, m), 4.44-4.68 (3H, m), 6.88-7.04 (2H, m), 7.23-7.31 (2H, m), 7.32-7.40 (1H, m), 7.41-7.62 (3H, m), 7.63-7.72 (1H, m)
167		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.73-0.86 (2H, m), 1.06-1.12 (2H, m), 1.76-1.88 (1H, m), 1.94-2.08 (2H, m), 2.11-2.44 (5H, m), 3.05-3.19 (2H, m), 3.42-3.51 (0.5H, m), 3.59-4.10 (3.5H, m), 4.56-4.78 (3H, m), 5.40-5.94 (2H, brs), 6.67-6.74 (1H, m), 7.12-7.22 (1H, m), 7.31-7.40 (1H, m), 7.41-7.60 (2H, m), 7.64-7.73 (1H, m), 7.91-7.99 (1H, m), 8.56-8.63 (1H, m)

Table 1-41

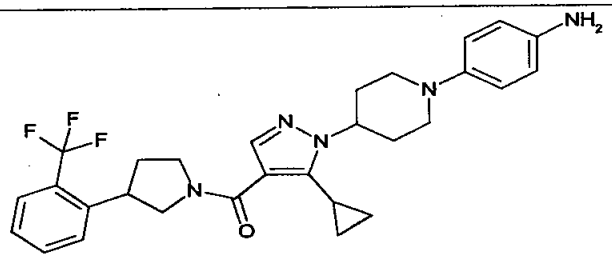
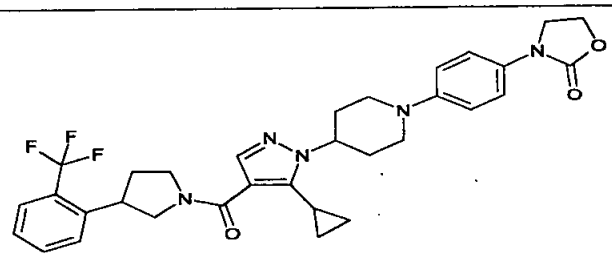
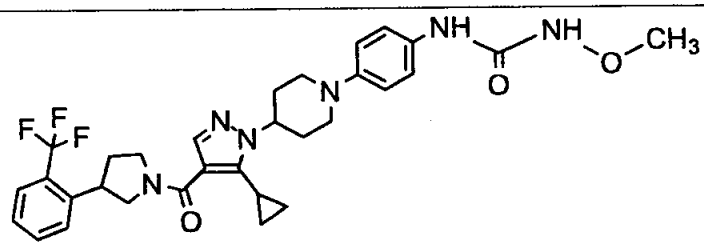
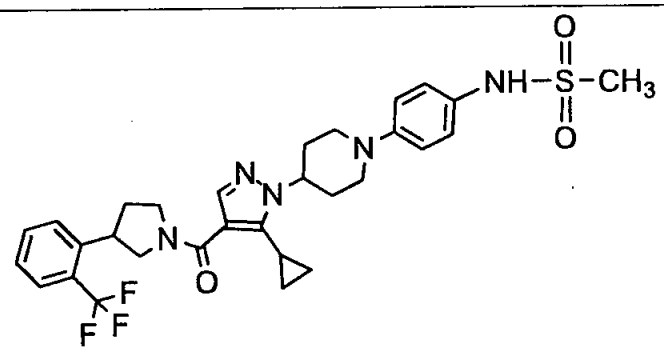
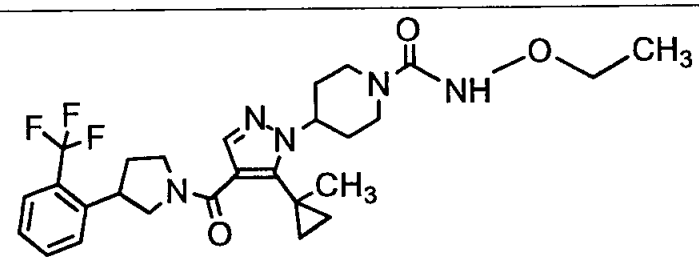
Ex. No.	structural formula	NMR
168		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.85 (2H, m), 1.02-1.14 (2H, m), 1.73-1.88 (1H, m), 1.90-2.22 (3H, m), 2.27-2.51 (3H, m), 2.71-2.88 (2H, m), 3.35-4.11 (9H, m), 4.38-4.56 (1H, m), 6.60-6.71 (2H, m), 6.78-6.91 (2H, m), 7.31-7.40 (1H, m), 7.41-7.62 (3H, m), 7.63-7.71 (1H, m)
169		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.88 (2H, m), 1.02-1.16 (2H, m), 1.73-1.88 (1H, m), 1.91-2.19 (3H, m), 2.27-2.50 (3H, m), 2.81-3.00 (2H, m), 3.40-4.17 (9H, m), 4.39-4.63 (3H, m), 6.92-7.04 (2H, m), 7.31-7.72 (7H, m)
170		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.86 (2H, m), 1.01-1.16 (2H, m), 1.72-1.88 (1H, m), 1.91-2.23 (3H, m), 2.26-2.51 (3H, m), 2.76-2.98 (2H, m), 3.42-4.11 (10H, m), 4.42-4.62 (1H, m), 6.89-7.00 (2H, m), 7.16 (1H, s), 7.31-7.73 (8H, m)
171		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.86 (2H, m), 1.00-1.16 (2H, m), 1.72-1.88 (1H, m), 1.92-2.23 (3H, m), 2.26-2.48 (3H, m), 2.84-3.02 (5H, m), 3.38-4.12 (7H, m), 4.45-4.65 (1H, m), 6.25-6.38 (1H, m), 6.88-6.99 (2H, m), 7.11-7.22 (2H, m), 7.32-7.40 (1H, m), 7.41-7.62 (3H, m), 7.63-7.71 (1H, m)
172		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-1.01 (4H, m), 1.16-1.35 (3H, m), 1.35-1.53 (3H, m), 1.71-1.97 (2H, m), 1.97-2.49 (4H, m), 2.86-3.09 (2H, m), 3.41-4.31 (9H, m), 4.53-4.75 (1H, m), 7.17-7.30 (1H, m), 7.30-7.40 (1H, m), 7.41-7.60 (3H, m), 7.61-7.74 (1H, m)

Table 1-42

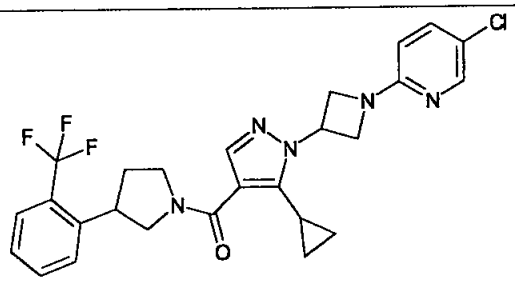
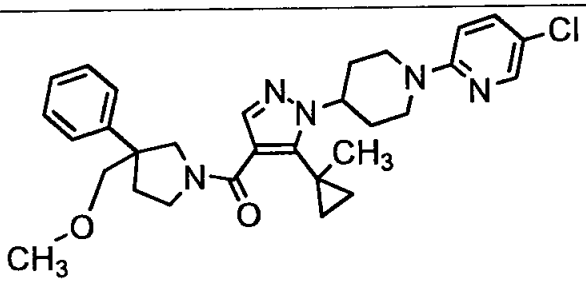
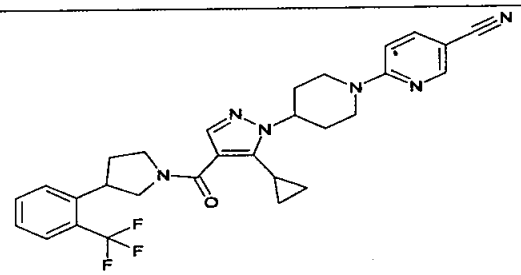
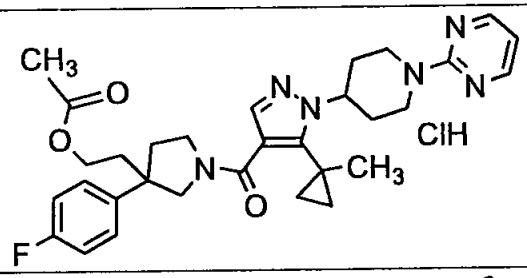
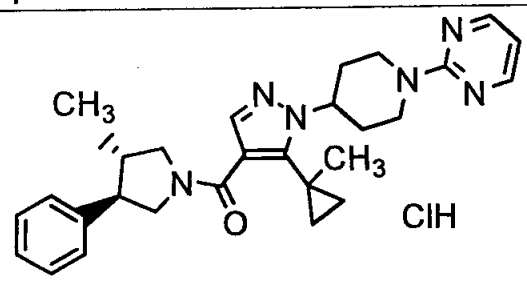
Ex. No.	structural formula	NMR
173		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.61-0.87 (2H, m), 1.00-1.19 (2H, m), 1.57-1.87 (1H, m), 1.93-2.25 (1H, m), 2.25-2.48 (1H, m), 3.31-4.15 (5H, m), 4.35-4.59 (4H, m), 5.44-5.66 (1H, m), 6.26-6.40 (1H, m), 7.30-7.76 (6H, m), 8.02-8.17 (1H, m)
174		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.93 (4H, m), 1.41-1.52 (3H, m), 1.83-2.01 (2H, m), 2.13-2.51 (4H, m), 2.97-3.11 (2H, m), 3.16-4.12 (9H, m), 4.41-4.54 (2H, m), 4.65-4.78 (1H, m), 6.62-6.71 (1H, m), 7.12-7.55 (7H, m), 8.10-8.16 (1H, m)
175		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.72-0.85 (2H, m), 1.04-1.16 (2H, m), 1.73-1.88 (1H, m), 1.94-2.09 (2H, m), 2.10-2.45 (5H, m), 3.07-3.22 (2H, m), 3.42-3.51 (0.5H, m), 3.57-4.10 (3.5H, m), 4.52-4.80 (3H, m), 6.62-6.71 (1H, m), 7.32-7.41 (1H, m), 7.41-7.72 (5H, m), 8.38-8.45 (1H, m)
176		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.46-0.86 (4H, m), 1.07-1.24 (2H, m), 1.27-1.41 (3H, m), 1.73-2.07 (7H, m), 2.15-2.30 (2H, m), 3.06-4.08 (8H, m), 4.72-4.88 (3H, m), 6.66-6.74 (1H, m), 7.08-7.61 (5H, m), 8.38-8.48 (2H, m)
177		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.70-0.97 (7H, m), 1.35-1.42 (3H, m), 1.86-2.03 (4H, m), 2.25-2.46 (1H, m), 2.84-2.95 (1H, m), 3.07-3.24 (3H, m), 3.39-3.57 (1H, m), 3.67-3.77 (1H, m), 3.81-3.94 (1H, m), 4.75-4.88 (3H, m), 6.64-6.72 (1H, m), 7.20-7.41 (5H, m), 7.53-7.61 (1H, m), 8.39-8.44 (2H, m)

Table 1-43

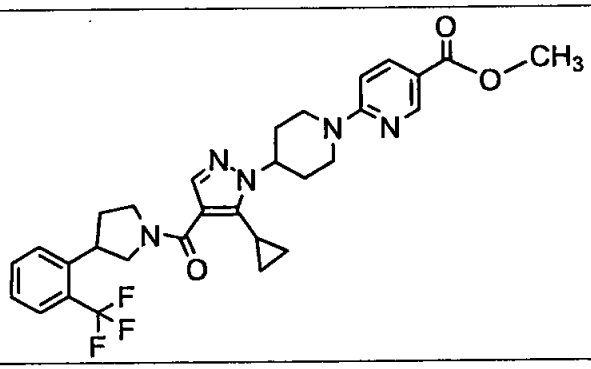
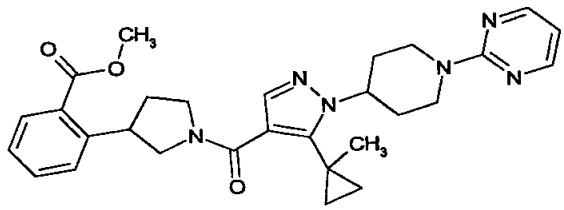
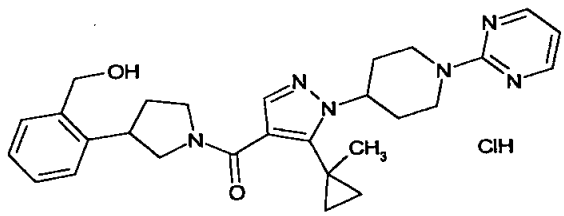
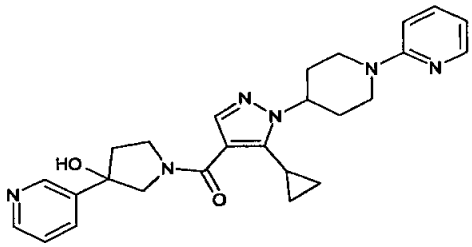
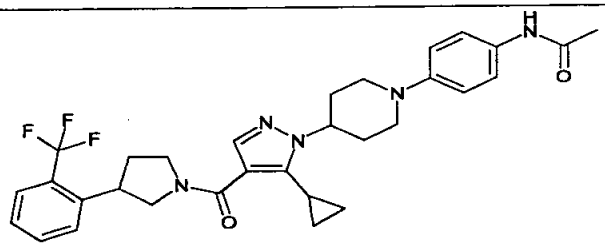
Ex. No.	structural formula	NMR
178		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.74-0.86 (2H, m), 1.05-1.15 (2H, m), 1.76-1.88 (1H, m), 1.93-2.09 (3H, m), 2.11-2.46 (4H, m), 3.04-3.19 (2H, m), 3.43-3.51 (0.5H, m), 3.59-4.09 (3.5H, m), 3.84-3.91 (3H, s), 4.58-4.78 (3H, m), 6.61-6.71 (1H, m), 7.32-7.61 (3.5H, m), 7.63-7.71 (1H, m), 7.98-8.08 (1.5H, m), 8.77-8.83 (1H, m)
179		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.77-0.98 (4H, m), 1.44-1.53 (3H, m), 1.86-2.46 (6H, m), 2.99-3.15 (2H, m), 3.45-4.06 (7H, m), 4.18-4.41 (1H, m), 4.68-4.85 (1H, m), 4.94-5.09 (2H, m), 6.48-6.55 (1H, m), 7.26-7.56 (4H, m), 7.82-7.92 (1H, m), 8.31-8.37 (2H, m)
180		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.67-0.91 (4H, m), 1.29-1.44 (3H, m), 1.74-2.34 (7H, m), 3.02-4.18 (7H, m), 4.47-4.69 (2H, m), 4.77-4.91 (3H, m), 6.60-6.71 (1H, m), 7.14-7.69 (5H, m), 8.34-8.46 (2H, m)
181		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.77 (2H, m), 0.99-1.15 (2H, m), 1.75-1.89 (1H, m), 1.92-2.05 (2H, m), 2.18-2.53 (4H, m), 2.96-3.09 (2H, m), 3.68-3.85 (2H, m), 3.87-4.04 (2H, m), 4.44-4.56 (2H, m), 4.58-4.72 (1H, m), 6.58-6.67 (1H, m), 6.68-6.76 (1H, m), 7.29-7.39 (1H, m), 7.45-7.53 (2H, m), 7.75-7.88 (1H, m), 8.17-8.23 (1H, m), 8.54-8.62 (1H, m), 8.69-8.83 (1H, m)
182		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.83 (2H, m), 1.01-1.15 (2H, m), 1.69-1.88 (1H, m), 1.90-2.21 (6H, m), 2.26-2.50 (3H, m), 2.77-3.00 (2H, m), 3.41-4.11 (7H, m), 4.40-4.62 (1H, m), 6.85-6.97 (2H, m), 7.31-7.71 (7H, m)

Table 1-44

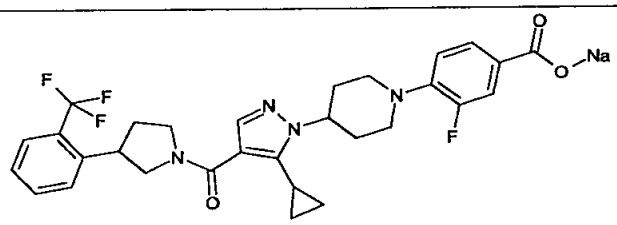
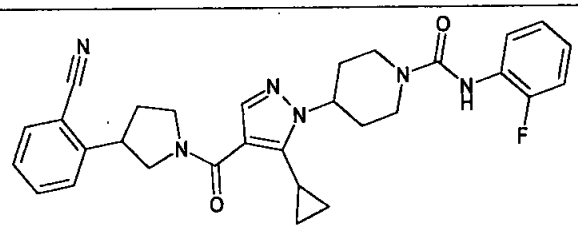
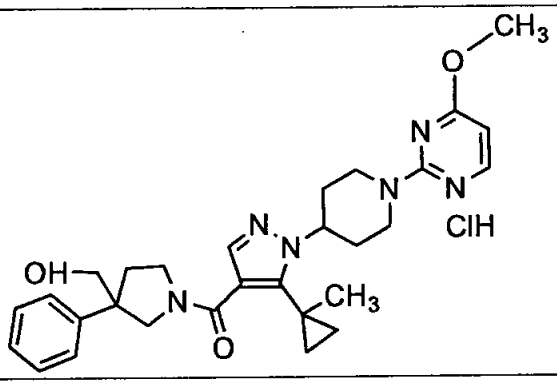
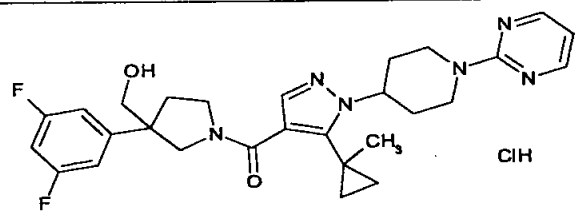
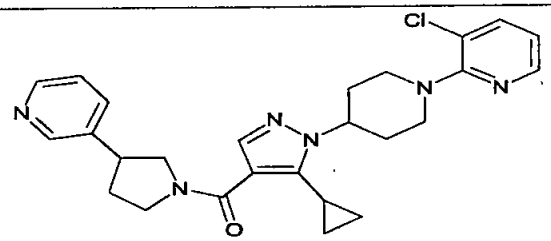
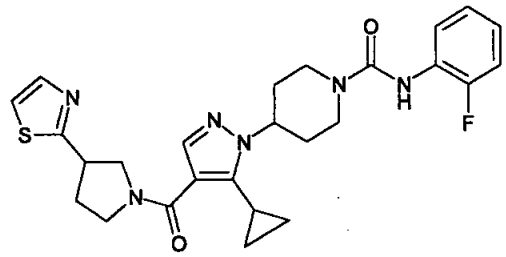
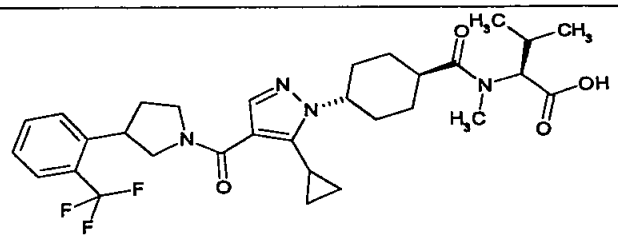
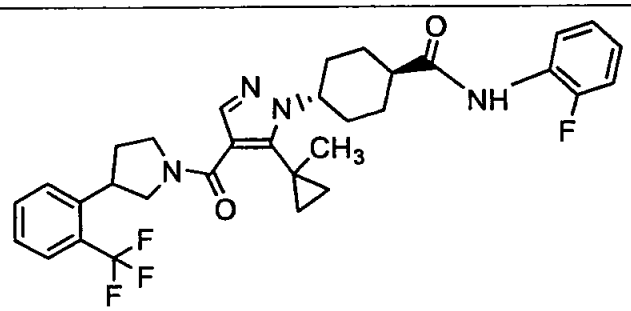
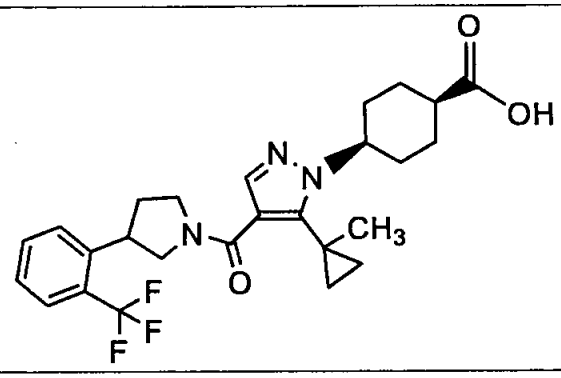
Ex. No.	structural formula	NMR
183		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.60-0.75 (2H, m), 0.94-1.06 (2H, m), 1.88-2.34 (7H, m), 2.79-2.98 (2H.m), 3.44-3.93 (7H, m), 4.50-4.68 (1H, m), 6.89-7.03 (1H, m), 7.43-7.80 (7H, m)
184		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.86 (2H, m), 1.05-1.16 (2H, m), 1.77-1.88 (1H, m), 1.94-2.53 (6H, m), 3.06-3.22 (2H, m), 3.45-4.16 (5H, m), 4.21-4.35 (2H, m), 4.57-4.73 (1H, m), 6.67 (1H, s), 6.95-7.17 (3H, m), 7.35-7.73 (5H, m), 8.05-8.13 (1H, m)
185		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.58-0.88 (4H, m), 1.29-1.44 (3H, m), 1.94-2.21 (5H, m), 2.28-2.41 (1H, m), 3.27-3.93 (8H, m), 3.95-4.05 (3H, m), 4.58-4.97 (3H, m), 5.42-6.26 (1H, m), 6.37-6.50 (1H, m), 7.14-7.41 (5H, m), 7.53-7.68 (1H, m), 8.11-8.23 (1H, m)
186		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.55-0.85 (4H, m), 1.32-1.41 (3H, m), 1.84-2.40 (7H, m), 3.06-3.23 (2H, m), 3.29-3.90 (5H, m), 4.72-4.88 (3H, m), 4.89-5.35 (2H, m), 6.66-6.72 (1H, m), 6.91-7.64 (4H, m), 8.39-8.44 (2H, m)
187		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.85 (2H, m), 1.01-1.13 (2H, m), 1.57-1.88 (2H, m), 1.93-2.20 (1H, m), 2.33-2.56 (3H, m), 2.94-3.07 (2H, m), 3.35-3.82 (4H, m), 3.86-4.21 (4H, m), 4.52-4.66 (1H, m), 6.82-6.88 (1H, m), 7.24-32 (3H, m), 7.55-7.64 (3H, m), 8.15-8.22 (1H, m), 8.47-8.61 (1H, m)

Table 1-45

Ex. No.	structural formula	NMR
188		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.78 (2H, m), 0.96-1.11 (2H, m), 1.71-1.85 (1H, m), 1.92-2.09 (3H, m), 2.16-2.57 (4H, m), 3.04-3.21 (2H, m), 3.55-4.00 (4H, m), 4.19-4.34 (2H, m), 4.54-4.68 (1H, m), 6.61-6.70 (1H, m), 6.91-7.15 (3H, m), 7.23-7.31 (1H, m), 7.51-7.58 (1H, m), 7.67-7.76 (1H, m), 8.03-8.12 (1H, m)
189		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.53-0.69 (2H, m), 0.71-0.88 (2H, m), 0.91-1.11 (6H, m), 1.43-2.39 (10H, m), 2.62-2.82 (2H, m), 2.92-3.06 (3H, m), 3.42-3.92 (6H, m), 4.10-4.74 (2H, m), 7.39-7.59 (2H, m), 7.63-7.81 (2H, m)
190		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.73-0.97 (4H, m), 1.36-1.51 (3H, m), 1.77-1.95 (2H, m), 1.97-2.26 (7H, m), 2.29-2.49 (2H, m), 3.47-4.11 (5H, m), 4.46-4.64 (1H, m), 7.00-7.20 (3H, m), 7.32-7.72 (6H, m), 8.29-8.42 (1H, m)
191		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.73-0.97 (4H, m), 1.38-1.49 (3H, m), 1.60-1.76 (1H, m), 1.77-1.90 (2H, m), 1.93-2.18 (2H, m), 2.19-2.56 (5H, m), 2.70-2.81 (1H, m), 3.47-4.09 (5H, m), 4.42-4.61 (1H, m), 7.31-7.72 (5H, m)

The present invention is now concretely explained by way of the following Formulation Examples, which are not to be construed as limitative.

Formulation Example 1 (production of capsule)

1) Compound of Example 1	30 mg
2) crystalline cellulose	10 mg
3) lactose	19 mg
4) magnesium stearate	1 mg

1), 2), 3) and 4) were mixed and filled in a gelatin capsule.

Formulation Example 2 (production of tablet)

1) Compound of Example 1	30 g
2) lactose	50 g
3) cornstarch	15 g
4) carboxymethylcellulose calcium	44 g
5) magnesium stearate	1 g

The entire amount of 1), 2), 3) and 30 g of 4) are kneaded with water, dried under reduced pressure and sized. The sized powder is mixed with 14 g of 4) and 1 g of 5), and tableted with a tableting machine. In this way, 1000 tablets containing 30 mg of the compound of Example 1 per tablet are obtained.

In the same manner as in the above-mentioned Formulation Example 1 or Formulation Example 2, the compounds of Examples 2 to 191 can also be used to produce capsules or tablets.

Experimental Example 1: HSD-1 (hydroxysteroid dehydrogenase 1) activity inhibitory action in vitro

The HSD-1 activity inhibitory action was determined by quantitation of inhibition of conversion of cortisone to cortisol by SPA (scintillation proximity assay) system and using, as an enzyme source, human HSD-1 (hereinafter recombinant HSD-1) expressed using baculovirus system. Reagents (100 µl) were added to a 96 well plate (96 well Opti-plates™-96 (Packard)) to a final concentration shown below and the reaction was carried out at room temperature for 90 to 120 min. As a reaction mixture, 5-100 ng/well recombinant HSD-1, 500 µM NADPH and 10 nM ^{3}H cortisone (American Radiolabeled Chemicals Inc., 50 Ci/mmol) were dissolved in PBS containing

0.1% BSA (Sigma), and the test substance was 2 μl of a compound solution (dissolved in DMSO). After the reaction, 50 μl of PBS (containing 0.1% BSA (Sigma)) containing 0.2 μg of anti-cortisol mouse monoclonal antibody (East Coast Biologics), 500 μg of anti-mouse antibody bonded PVT SPA beads (Amersham Biosciences) and 133 μM carbenoxolone (Sigma) was added to the reaction mixture to stop the reaction. After completion of the reaction, the mixture was incubated at room temperature for not less than 2 hr, and the radioactivity was measured with Topcount (Packard). As the control, the value of the well added with 2 μl of DMSO instead of the test substance was used (0% inhibition) and, as the positive control, the value of the well added with carbenoxolone (final concentration 100 μM) instead of the test substance was used (100% inhibition). inhibition (%) of the test substance was calculated from ((value of control - value of test substance)/(value of control - value of positive control)) ×100(%). The IC_{50} value was calculated from the inhibition rates of two points across the 50% inhibition. The obtained results are shown in the following Table 2-1 to Table 2-3.

Table 2-1

Ex. No.	hHSD1 (IC_{50} (nM))	Ex. No.	hHSD1 (IC_{50} (nM))
2	++	41	++
3	++	42	++
4	++	43	++
6	++	44	++
7	++	45	++
8	++	47	++
9	++	48	++
10	++	49	++
11	++	50	++
12	++	51	++
13	++	52	++
14	++	53	++
15	++	54	++
16	++	55	++
17	++	56	++
18	++	57	++
19	++	58	++
20	++	59	++
21	++	60	++
22	++	61	++
23	++	63	++
24	++	64	++
25	++	65	++
26	++	66	++
27	++	67	++
28	++	68	++
29	++	69	++
30	++	71	++
31	++	72	++
32	++	73	++
33	++	74	++
34	++	75	++
35	++	76	++
36	++	77	++
37	++	78	++
39	++	79	++
40	++	80	++

Table 2-2

Ex. No.	hHSD1 (IC_{50} (nM))	Ex. No.	hHSD1 (IC_{50} (nM))
83	++	130	++
84	++	131	++
85	++	132	++
87	++	133	++
88	++	134	++
89	++	135	++
90	++	136	++
91	++	137	++
93	++	138	++
94	++	139	++
95	++	140	++
96	++	141	++
97	++	142	++
99	++	145	++
100	++	146	++
103	++	147	++
105	++	148	++
106	++	149	++
107	++	150	++
108	++	151	++
109	++	154	++
110	++	155	++
111	++	156	++
112	++	157	++
113	++	158	++
114	++	165	++
115	++	166	++
116	++	167	++
117	++	168	++
118	++	169	++
119	++	170	++
120	++	171	++
124	++	172	++
125	++	173	++
126	++	174	++
128	++	175	++
129	++	176	++

Table 2-3

Ex. No.	hHSD1 (IC_{50} (nM))	Ex. No.	hHSD1 (IC_{50} (nM))
177	++	185	++
178	++	186	++
179	++	187	++
180	++	189	++
182	++	190	++
183	++	191	++
184	++		

In the above-mentioned Tables, ++ means IC_{50} value of not more than 30 nM.

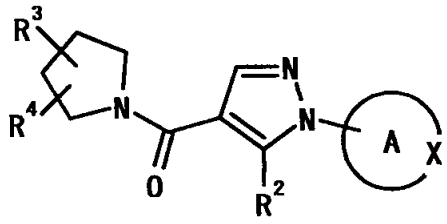
Industrial Applicability

The heterocyclic compound of the present invention has a superior HSD1 inhibitory action and is useful as an agent for the prophylaxis or treatment of metabolic diseases such as diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension, fatty liver and the like, and the like, and the like.

This application is based on patent application Nos. 2005-168901, 2006-027097 and 2006-138252 filed in Japan, and 60/692,039 and 60/772,734 filed in the US, the contents of which are incorporated in full herein by this reference.

CLAIMS

1. A compound represented by the following formula [1']:



[1']

wherein

ring A is

(1) a nitrogen-containing saturated monocyclic heterocyclic group, or

(2) a cycloalkyl group,

said ring A is optionally substituted by one or more, same or different substituents R^1,

said substituent R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the

following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group,

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

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

(h) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or a heterocyclic group which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic

heterocyclic group,

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

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms),

and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group, or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a $-COO-C_{1-6}$ alkyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(c) a cycloalkyl group,

(d) a halogen atom,

(e) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a $-COO-C_{1-6}$ alkyl group,

(g) a cyano group, and

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

-X- is

(1) $-N(R^1)-$ wherein R^1 is as defined above, or

(2) $-C(R^7R^8)-$ wherein R^7 and R^8 are the same or different and each is

1) a hydrogen atom,

2) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or $-CO-NR^{36}R^{37}$ wherein R^{36} and R^{37} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{36} and R^{37} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group), or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

3) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more carboxyl groups), or an aryl group (said aryl group is optionally

substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, and (b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group, or

5) a carboxyl group;

R^2 is

(1) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a hydroxyl group, and (b) a C_{1-6} alkoxy group), and 2) a C_{1-6} alkoxy group); and

R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, 2) a hydroxyl group, 3) a C_{1-6} alkoxy group, and 4) a $-OCO-C_{1-6}$ alkyl group),

(3) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following 1) to 6):

1) a halogen atom,

2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, (b) a hydroxyl group, and (c) a C_{1-6} alkoxy group),

3) a C_{1-6} alkoxy group (said C_{1-6} alkoxy group is optionally substituted by one or more, same or different

halogen atoms),

4) a carboxyl group,

5) a $-COO-C_{1-6}$ alkyl group, and

6) a cyano group),

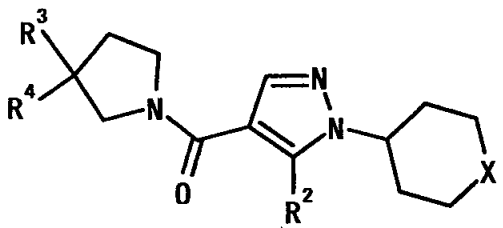
(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

(5) a hydroxyl group, or

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

or a salt thereof.

2. A compound represented by the following formula [1]:



[1]

wherein

-X- is

(1) $-N(R^1)-$ wherein R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally

substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or

different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group,

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

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

(h) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or a heterocyclic group which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic

heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl

group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6}

alkyl group is optionally substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group, or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or

R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a $-COO-C_{1-6}$ alkyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(c) a cycloalkyl group,

(d) a halogen atom,

(e) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a $-COO-C_{1-6}$ alkyl group,

(g) a cyano group, and

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

(2) $-C(R^7R^8)-$ wherein R^7 and R^8 are the same or different and each is

1) a hydrogen atom,

2) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or $-CO-NR^{36}R^{37}$ wherein R^{36} and R^{37} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{36} and R^{37} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or R^{16} and R^{17} optionally form, together with the nitrogen atom

bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

3) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more carboxyl groups), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, and (b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group, or

5) a carboxyl group;

R^2 is

(1) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a hydroxyl group, and (b) a C_{1-6} alkoxy group), and 2) a C_{1-6} alkoxy group); and

R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, 2) a hydroxyl group, 3) a C_{1-6} alkoxy group, and 4) a $-OCO-C_{1-6}$ alkyl group),

(3) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following 1) to 6):

1) a halogen atom,

2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, (b) a hydroxyl group, and (c) a C_{1-6} alkoxy group),

3) a C_{1-6} alkoxy group (said C_{1-6} alkoxy group is optionally substituted by one or more, same or different halogen atoms),

4) a carboxyl group,

5) a $-COO-C_{1-6}$ alkyl group, and

6) a cyano group),

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

(5) a hydroxyl group, or

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

or a salt thereof.

3. The compound of any one of claims 1 and 2, wherein -X- is $-C(R^7R^8)-$ wherein R^7 and R^8 are as defined in claim 1, or a salt thereof.

4. The compound of any one of claims 1 to 3, wherein R^8 is

1) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

2) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

3) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group,

or a salt thereof.

5. The compound of claim 1 or 2, wherein -X- is $-N(R^1)-$ wherein R^1 is as defined in claim 1, or a salt thereof.

6. The compound of any one of claims 1, 2 and 5, wherein R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group) and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(h) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic

heterocyclic group,

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

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is

a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group, or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a $-COO-C_{1-6}$ alkyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(c) a cycloalkyl group, and

(d) a halogen atom,

(e) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a $-COO-C_{1-6}$ alkyl group,

(g) a cyano group, and

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

or a salt thereof.

7. The compound of any one of claims 1, 2 and 5, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

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

(h) a nitrogen-containing unsaturated monocyclic

heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not any combination of substituents selected from the following group: (i) a hydrogen atom, and (ii) an unsubstituted C_{1-6} alkyl group),

2) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents

selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from

the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

5) a cycloalkyl group,

6) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

7) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

8) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

9) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following (a) to (g):

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(b) a cycloalkyl group,

(c) a halogen atom,

(d) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(e) a $-COO-C_{1-6}$ alkyl group,

(f) a cyano group, and

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

or a salt thereof.

8. The compound of any one of claims 1, 2 and 5, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents

selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2):

(1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group, and

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(h) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$

alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms),

2) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic

heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different -CO-$NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) -CO-$NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

5) a cycloalkyl group,

6) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents

selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

7) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

8) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

9) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following (a) to (g):

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(b) a cycloalkyl group,

(c) a halogen atom,

(d) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(e) a $-COO-C_{1-6}$ alkyl group,

(f) a cyano group, and

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

or a salt thereof.

9. The compound of any one of claims 1 to 8, wherein R^2 is a cyclopropyl group or a 1-methylcyclopropyl group, or a salt thereof.

10. The compound of any one of claims 1 to 9, wherein R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a $-OCO-C_{1-6}$ alkyl group),

(3) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following 1) to 5):

1) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, and (b) a hydroxyl group),

2) a C_{1-6} alkoxy group (said C_{1-6} alkoxy group is substituted by one or more, same or different halogen atoms),

3) a carboxyl group,

4) a $-COO-C_{1-6}$ alkyl group, and

5) a cyano group), or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

(provided that R^3 and R^4 are not simultaneously hydrogen atoms),

or a salt thereof.

11. The compound of claim 1, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the

following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

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

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

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

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

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

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

(h) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or

different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms),

2) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

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

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a

C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

5) a cycloalkyl group,

6) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

7) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

8) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

9) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group), or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic

group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a $-COO-C_{1-6}$ alkyl group), or

10) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

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

(c) a cycloalkyl group,

(d) a halogen atom,

(e) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(f) a $-COO-C_{1-6}$ alkyl group,

(g) a cyano group, and

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

or a salt thereof.

12. The compound of claim 1, or a salt thereof, which is selected from the following:

(1) 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine,

(2) 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-

carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(3) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(4) 1-[1-(1-carbamoylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(5) 1-{1-[1-(2-carboxyphenylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(6) 1-{5-cyclopropyl-1-[1-(2-hydroxymethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(7) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(8) 1-{5-cyclopropyl-1-[1-(2-hydroxyethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(9) 1-{5-cyclopropyl-1-[1-(2-hydroxy-1,1-dimethylethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(10) 1-{1-[1-(2-acetylaminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(11) 1-{1-[1-(2-aminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(12) 1-{5-cyclopropyl-1-[1-(1,1-dioxothiomorpholine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(13) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(14) 1-{5-cyclopropyl-1-[1-(4-hydroxypiperidine-1-

carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(15) 1-{1-[1-(azetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(16) 1-{5-cyclopropyl-1-[1-(3-hydroxypyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(17) 1-{5-cyclopropyl-1-[1-(2-piperidin-1-yl-ethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(18) 1-{5-cyclopropyl-1-[1-(4,4-difluoropiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(19) 1-{5-cyclopropyl-1-[1-(3,3-difluoropyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(20) 1-{5-cyclopropyl-1-[1-(3-hydroxyazetidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(21) 1-(5-cyclopropyl-1-{1-[(R)-3-hydroxypyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(22) 1-(5-cyclopropyl-1-{1-[(S)-3-hydroxypyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(23) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxy-1-methylethylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(24) 1-{5-cyclopropyl-1-[1-(4-hydroxymethylpiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(25) 1-{1-[1-(4-carboxypiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(26) 1-{5-cyclopropyl-1-[1-(3-oxopiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(27) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxymethylpyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(28) 1-{5-cyclopropyl-1-[1-(3-hydroxymethylazetidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(29) 1-{5-cyclopropyl-1-[1-(4-methylpiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(30) 1-{5-cyclopropyl-1-[1-(4-isopropylpiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(31) 1-{1-[1-(4-acetylpiperazine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(32) 1-(5-cyclopropyl-1-{1-[(R)-3-hydroxypiperidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(33) 1-{1-[1-(4-carbamoylpiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(34) 1-{1-[1-(3-carbamoylazetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(35) 1-{1-[1-(4-aminopiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(36) 1-{1-[1-(3-aminopyrrolidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(37) 1-{5-cyclopropyl-1-[1-(piperidin-4-yl-carbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine hydrochloride,
(38) 1-{5-cyclopropyl-1-[1-(4-dimethylaminopiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(39) 1-{1-[1-(4-acetylaminopiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(40) 1-{1-[1-(3-acetylaminopyrrolidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(41) 1-{5-cyclopropyl-1-[1-(3-dimethylaminopyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(42) 1-{5-cyclopropyl-1-[1-(1-methylpiperidin-4-yl-carbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(43) 1-{1-[1-(1-acetylpiperidin-4-yl-carbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(44) 1-{5-cyclopropyl-1-[1-(4-oxopiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(45) 1-{1-[1-(3-acetylaminoazetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(46) 1-{5-cyclopropyl-1-[1-(3-oxopyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(47) 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(48) 1-{5-cyclopropyl-1-[1-(3,3,4,4-tetrafluoropyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(49) 1-(5-cyclopropyl-1-{1-[(S)-1-hydroxymethyl-2-

methylpropylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(50) 1-(1-{1-[(S)-1-benzyl-2-hydroxyethylcarbamoyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(51) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxy-1-phenylethylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(52) 1-(5-cyclopropyl-1-{1-[(S)-1-hydroxymethyl-3-methylbutylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(53) 1-{5-cyclopropyl-1-[1-(2-hydroxyphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(54) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopentylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(55) 1-[1-(1-benzenesulfonylaminocarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(56) 1-[5-cyclopropyl-1-(1-methanesulfonylaminocarbonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(57) 1-[5-cyclopropyl-1-(1-methoxycarbonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(58) 1-{5-cyclopropyl-1-[1-(2-hydroxyethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(59) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(60) 1-{5-cyclopropyl-1-[1-(2-piperidin-1-yl-ethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-

(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(61) 1-{5-cyclopropyl-1-[1-(piperidin-4-yl-oxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(62) 1-{5-cyclopropyl-1-[1-(1-methylpiperidin-4-yl-oxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(63) 1-{1-[1-(1-acetylpiperidin-4-yl-oxycarbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(64) 1-[1-(1-cyclopropanecarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(65) 1-{5-cyclopropyl-1-[1-(2-hydroxyacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(66) 1-(5-cyclopropyl-1-{1-[1-(4-fluorophenyl)cyclopropanecarbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(67) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(68) 1-{1-[1-(2-acetylaminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(69) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropanecarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(70) 1-{1-[1-(2-acetylamino-2-methylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(71) 1-(1-{1-[(S)-2-acetylaminopropionyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(72) 1-(1-{1-[(S)-2-acetylamino-3-methylbutyryl]piperidin-4-

yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(73) 1-{5-cyclopropyl-1-[1-(3,3,3-trifluoropropionyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(74) 1-(5-cyclopropyl-1-{1-[(S)-5-oxopyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(75) 1-{1-[1-(3-acetylaminopropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(76) 1-{5-cyclopropyl-1-[1-(3-hydroxy-2,2-dimethylpropionyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(77) 1-{1-[1-(2-aminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(78) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopropanecarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(79) 1-{1-[1-(2-amino-2-methylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(80) 1-{5-cyclopropyl-1-[1-(4-hydroxybutyryl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(81) 1-(5-cyclopropyl-1-{1-[(S)-pyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(82) 1-(5-cyclopropyl-1-{1-[(S)-1-methylpyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(83) 1-{1-[1-(3-aminopropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(84) 1-(1-{1-[(S)-2-amino-3-methylbutyryl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(85) 1-{5-cyclopropyl-1-[1-(2-methylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(86) 1-{5-cyclopropyl-1-[1-(piperidine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(87) 1-{5-cyclopropyl-1-[1-(2-isobutyrylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(88) 1-{1-[1-(2-cyclopropanecarbonylaminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(89) 1-(1-{1-[(S)-1-acetylpyrrolidine-2-carbonyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(90) 1-{5-cyclopropyl-1-[1-(2-methanesulfonylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(91) 1-{1-[1-(1-acetylpiperidine-4-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(92) 1-{5-cyclopropyl-1-[1-(1-methylpiperidine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(93) 1-{1-[1-(3-carbamoylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(94) 1-[1-(1-carbamoylmethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(95) 1-[5-cyclopropyl-1-(1-methylcarbamoylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine hydrochloride,
(96) 1-{1-[1-(1-carbamoyl-1-methylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(97) 1-{1-[1-(2-carbamoylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(98) 1-[5-cyclopropyl-1-(1-cyclopropylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(99) 1-[5-cyclopropyl-1-(1-cyclopropylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(100) 1-[5-cyclopropyl-1-(1-dimethylcarbamoylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(101) 1-[1-(1-carboxymethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(102) 1-[1-(1-carboxyethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(103) 1-{1-[1-(1-carbamoylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(104) 1-{1-[1-(2-carboxy-2-methylpropyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(105) 1-{1-[1-(2-carbamoyl-2-methylpropyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(106) 1-{1-[1-(1-carbamoylcyclopropylmethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(107) 1-(5-cyclopropyl-1-{1-[1-(2-

hydroxyethylcarbamoyl)cyclopropylmethyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(108) 1-[5-cyclopropyl-1-(1-trifluoromethanesulfonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(109) 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethanesulfonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(110) 1-{1-[1-(1-cyanoiminoethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(111) 1-(1-{1-[cyanoimino(methylamino)methyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(112) 1-{1-[1-(N-cyanocarbamimidoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(113)4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid,

(114)3-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid,

(115)5-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiophene-2-carboxylic acid,

(116)2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiazole-4-carboxylic acid,

(117) 1-{5-cyclopropyl-1-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(118) 1-{5-cyclopropyl-1-[1-(5-cyclopropyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine hydrochloride,
(119) 1-{5-cyclopropyl-1-[1-(5-hydroxymethyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(120) 1-{5-cyclopropyl-1-[1-(5-trifluoromethyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(121) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(122) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(123) 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(124) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(125) 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(126) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(127) (-)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,
(128) (+)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,
(129) 1-[5-cyclopropyl-1-(1-pyrazin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(130) 1-[1-(trans-4-carbamoylcyclohexyl)-5-cyclopropyl-1H-

pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(131) 1-[5-cyclopropyl-1-(trans-4-ureidocyclohexyl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(132) 1-{5-cyclopropyl-1-[trans-4-(1H-tetrazol-5-yl)cyclohexyl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(133) 1-{5-(1-methylcyclopropyl)-1-[1-(4-trifluoromethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(134) 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-methoxycyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(135) 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-phenyl-3-trifluoromethyl-pyrrolidine,

(136) 3-(2-chlorophenyl)-1-{5-cyclopropyl-1-[1-(2,4-difluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine,

(137) 3-(2-chloropyridin-3-yl)-1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine,

(138) 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(2,2,3,3-tetramethylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(139) 1-{5-cyclohexyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(140) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethoxyphenyl)pyrrolidine,

(141) 1-{5-cyclopropyl-1-[1-(4-trifluoromethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(142) 1-(5-cyclopropyl-1-{1-[((S)-1-carboxy-2-methyl-

propyl)methylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(2-trifluoromethylphenyl)pyrrolidine,

(143) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-methoxy-3-(2-trifluoromethylphenyl)pyrrolidine,

(144) 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-hydroxymethylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(145) 1-{5-cyclopropyl-1-[1-(thiazol-2-ylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(146) 1-{1-[1-(isopropoxycarbamoyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(147) 1-{5-cyclopropyl-1-[1-(4-fluorobenzylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(148) 1-{1-[1-(2,3-dihydroindole-1-carbonyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(149) 1-{1-[1-(2,3-dihydro[1,4]oxazine-4-carbonyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(150) 1-{5-cyclopropyl-1-[1-(2,6-dichloropyridin-3-ylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(151) 1-{5-(1-methylcyclopropyl)-1-[1-(2,3,4,5-tetrahydrobenzo[b]azepine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(152) ethyl 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoate,

(153) 1-[1-(1-benzyloxycarbonyl-piperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine,

(154) 1-{1-[1-(3-carboxy-3-methyl-butyryl)piperidin-4-yl]-5-

cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(155) 1-{5-cyclopropyl-1-[1-(2-phenoxyacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(156) 1-{1-[1-(3-chlorobenzoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(157) 1-{1-[1-(2-chlorobenzoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(158) 1-[5-cyclopropyl-1-(1-oxalylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine,

(159) 1-{1-[1-(4-chlorobenzoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(160) 1-(5-cyclopropyl-1-{1-[2-(4-fluorophenyl)acetyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(pyridin-3-yl)pyrrolidine,

(161) 1-{5-cyclopropyl-1-[1-(3-trifluoromethylbenzoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(162) 1-{5-cyclopropyl-1-[1-(3-methoxybenzoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(163) 1-{1-[1-(4-fluorobenzyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine hydrochloride,

(164) 1-[1-(1-benzenesulfonyl-piperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine,

(165) 1-{1-[1-(4-carbamoylphenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(166) 1-{5-cyclopropyl-1-[1-(4-hydroxymethylphenyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(167) 1-{1-[1-(5-carbamoyl-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(168) 1-{1-[1-(4-aminophenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(169) 1-(5-cyclopropyl-1-{1-[4-(2-oxooxazolidin-3-yl)phenyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(2-trifluoromethylphenyl)pyrrolidine,

(170) 1-(5-cyclopropyl-1-{1-[4-(3-methoxyureido)phenyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(2-trifluoromethylphenyl)pyrrolidine,

(171) 1-{5-cyclopropyl-1-[1-(4-methanesulfonylaminophenyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(172) 1-[1-(1-ethoxycarbamoylpiperidin-4-yl)-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine,

(173) 1-[1-(5-chloropyridin-2-yl)azetidin-3-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine,

(174) 1-{1-[1-(5-chloro-pyridin-2-yl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-methoxymethyl-3-phenylpyrrolidine,

(175) 1-{1-[1-(5-cyano-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(176) 3-(2-acetoxyethyl)-3-(4-fluorophenyl)-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,

(177) {(3S*,4R*)-3-methyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-4-phenylpyrrolidine hydrochloride,

(178) methyl 6-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)nicotinate,

(179) methyl 2-{1-[5-(1-methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]pyrrolidin-3-yl}benzoate,

(180) 3-(2-hydroxymethylphenyl)-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,

(181) 1-[5-cyclopropyl-1-(1-pyridin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-hydroxy-3-(pyridin-3-yl)pyrrolidine,

(182) 1-{1-[1-(4-acetylaminophenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(183) sodium 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)-3-fluorobenzoate,

(184) 3-(2-cyanophenyl)-1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine,

(185) 3-hydroxymethyl-1-{1-[1-(4-methoxypyrimidin-2-yl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-phenylpyrrolidine hydrochloride,

(186) 3-(3,5-difluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,

(187) 1-{1-[1-(3-chloro-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(188) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(thiazol-2-yl)pyrrolidine,

(189) (S)-2-[(trans-4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)-pyrrolidine-1-carbonyl]-pyrazol-1-yl}-cyclohexanecarbonyl)-methyl-amino]-3-methylbutyric acid,

(190) 1-{5-(1-methylcyclopropyl)-1-[trans-4-(2-fluorophenylcarbamoyl)cyclohexyl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine, and

(191) cis-4-{5-(1-methylcyclopropyl)-4-[3-(2-trifluoromethylphenyl)-pyrrolidine-1-carbonyl]-pyrazol-1-yl)-cyclohexanecarboxylic acid.

13. A pharmaceutical composition comprising a compound of any one of claims 1 to 12 or a salt thereof.

14. A 11βHSD1 inhibitor comprising a compound of any one of claims 1 to 12 or a salt thereof.

15. An agent for the treatment or prophylaxis of a pathology involving glucocorticoid, which comprises a compound of any one of claims 1 to 12 or a salt thereof.

16. The agent of claim 15, wherein the pathology involving glucocorticoid is
(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,
(2) a metabolic syndrome,
(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,
(4) hyperorexia,
(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,
(6) a disease associated with decreased immune function,
(7) glaucoma, or
(8) osteoporosis.

17. A method of inhibiting 11βHSD1, which comprises administering a pharmaceutically effective amount of a compound of any one of claims 1 to 12 or a salt thereof.

18. A method of treating or preventing a pathology involving glucocorticoid, which comprises administering a pharmaceutically effective amount of a compound of any one of claims 1 to 12 or a salt thereof.

19. The method of claim 18, wherein the pathology involving glucocorticoid is
(1) a metabolic disease including diabetes, insulin resistance,

diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis.

20. Use of a compound of any one of claims 1 to 12 or a salt thereof for the production of a 11βHSD1 inhibitor.

21. Use of a compound of any one of claims 1 to 12 or a salt thereof for the production of an agent for the treatment or prophylaxis of a pathology involving glucocorticoid.

22. Use of claim 21, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis.

23. A commercial package comprising a written matter stating that the pharmaceutical composition of claim 13 can or should be used for the treatment or prophylaxis of a disease selected from

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis.

24. The pharmaceutical composition of claim 13 to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

25. The 11βHSD1 inhibitor of claim 14, to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,
(3) an agent for the treatment or prophylaxis of diabetes,
(4) an agent for the treatment or prophylaxis of diabetic complications,
(5) an agent for the treatment or prophylaxis of hypertension.

26. The agent of claim 15 or 16, which is to be used in combination with 1 to 3 agents selected from the following (1) to (5):
(1) an agent for the treatment or prophylaxis of hyperlipidemia,
(2) an agent for the treatment or prophylaxis of obesity,
(3) an agent for the treatment or prophylaxis of diabetes,
(4) an agent for the treatment or prophylaxis of diabetic complications,
(5) an agent for the treatment or prophylaxis of hypertension.

27. The method of claim 17, further comprising administering 1 to 3 agents selected from the following (1) to (5):
(1) an agent for the treatment or prophylaxis of hyperlipidemia,
(2) an agent for the treatment or prophylaxis of obesity,
(3) an agent for the treatment or prophylaxis of diabetes,
(4) an agent for the treatment or prophylaxis of diabetic complications,
(5) an agent for the treatment or prophylaxis of hypertension.

28. A pharmaceutical agent comprising 1 to 3 agents selected from the following (1) to (5) and a compound of any one of claims 1 to 12 or a salt thereof in combination:
(1) an agent for the treatment or prophylaxis of hyperlipidemia,
(2) an agent for the treatment or prophylaxis of obesity,
(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

29. A method of treating or preventing the pathology involving glucocorticoid of claim 18 or 19, which further comprises administering 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

30. The use of claim 20, which is to be combined with the use of 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

31. The use of claim 21 or 22, which is to be combined with the use of 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

32. The pharmaceutical composition of claim 13, which is used for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

33. The 11βHSD1 inhibitor of claim 14, which is used for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

34. The method of claim 17, which further comprises administering a pharmaceutical agent raising the blood glucocorticoid level.

35. The use of claim 21 for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

36. A method for suppressing the blood glucocorticoid level from rising, which comprises administering a pharmaceutical agent raising the blood glucocorticoid level and the 11βHSD1 inhibitor of claim 14.

37. Dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate.

38. Methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate.

39. (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one.

40. (S)-3-(2-trifluoromethylphenyl)pyrrolidine or a salt thereof.

41. A method for producing dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate, which comprises a step for reacting 1-((E)-2-nitrovinyl)-2-trifluoromethylbenzene with dimethyl malonate in the presence of 1-(3,5-bis-trifluoromethylphenyl)-3-((1S,2S)-2-dimethylaminocyclohexyl)-thiourea.

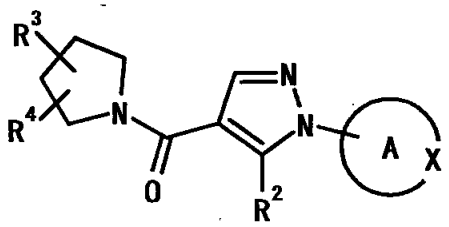
42. A method for producing methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate, which comprises a step for reduction and ring closure of dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate.

43. A method for producing (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one, which comprises a step for hydrolysis and decarbonation of methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate.

44. A method for producing a salt of (S)-3-(2-trifluoromethylphenyl)pyrrolidine, which comprises a step for reducing (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one and a step for treating the resulting compound with an acid to form a salt.

Abstract

The present invention provides a compound represented by the following formula [1'] or a salt thereof:



[1']

wherein ring A, R^2, R^3, R^4 and X are as defined in the description, and an agent for the treatment or prophylaxis of a pathology involving glucocorticoid, or a 11βHSD1 inhibitor, containing the compound or a salt thereof.

PCT REQUEST

0	**For receiving Office use only**	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	**Form PCT/RO/101 PCT Request**	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.51.022.197 MT/FOP 20070701/0.20.5.10
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	Japan Patent Office (RO/JP)
0-7	**Applicant's or agent's file reference**	09934e
I	**Title of Invention**	HETEROCYCLIC COMPOUND
II	**Applicant**	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
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II-5	Address	2-1, Toranomon 2-chome, Minato-ku, Tokyo 1058422 Japan
II-6	State of nationality	JP
II-7	State of residence	JP
II-8	Telephone No.	072-681-9720
II-9	Facsimile No.	072-681-9741
II-11	Applicant's registration No. with the Office	000004569

PCT REQUEST

III-1	**Applicant and/or inventor**	
III-1-1	This person is	applicant and inventor
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III-1-7	State of residence	JP
III-2	**Applicant and/or inventor**	
III-2-1	This person is	applicant and inventor
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III-2-6	State of nationality	JP
III-2-7	State of residence	JP
III-3	**Applicant and/or inventor**	
III-3-1	This person is	applicant and inventor
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III-3-5	Address	c/o Central Pharmaceutical Research Institute of Japan Tobacco Inc., 1-1, Murasaki-cho, Takatsuki-shi, Osaka 5691125 Japan
III-3-6	State of nationality	JP
III-3-7	State of residence	JP

PCT REQUEST

III-4	**Applicant and/or inventor**	
III-4-1	This person is	applicant and inventor
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III-4-4	Name (LAST, First)	HARADA, Kazuhito
III-4-5	Address	c/o Central Pharmaceutical Research Institute of Japan Tobacco Inc., 1-1, Murasaki-cho, Takatsuki-shi, Osaka 5691125 Japan
III-4-6	State of nationality	JP
III-4-7	State of residence	JP
III-5	**Applicant and/or inventor**	
III-5-1	This person is	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	YATA, Shinji
III-5-5	Address	c/o Central Pharmaceutical Research Institute of Japan Tobacco Inc., 1-1, Murasaki-cho, Takatsuki-shi, Osaka 5691125 Japan
III-5-6	State of nationality	JP
III-5-7	State of residence	JP
III-6	**Applicant and/or inventor**	
III-6-1	This person is	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	NISHIU, Jun
III-6-5	Address	c/o Central Pharmaceutical Research Institute of Japan Tobacco Inc., 1-1, Murasaki-cho, Takatsuki-shi, Osaka 5691125 Japan
III-6-6	State of nationality	JP
III-6-7	State of residence	JP

PCT REQUEST

III-7	**Applicant and/or inventor**	
III-7-1	This person is	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	KAKUTANI, Makoto
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III-7-6	State of nationality	JP
III-7-7	State of residence	JP
III-8	**Applicant and/or inventor**	
III-8-1	This person is	applicant and inventor
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III-8-4	Name (LAST, First)	FUJII, Shunsuke
III-8-5	Address	c/o Central Pharmaceutical Research Institute of Japan Tobacco Inc., 1-1, Murasaki-cho, Takatsuki-shi, Osaka 5691125 Japan
III-8-6	State of nationality	JP
III-8-7	State of residence	JP
III-9	**Applicant and/or inventor**	
III-9-1	This person is	applicant and inventor
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III-9-4	Name (LAST, First)	ASAHINA, Kota
III-9-5	Address	c/o Central Pharmaceutical Research Institute of Japan Tobacco Inc., 1-1, Murasaki-cho, Takatsuki-shi, Osaka 5691125 Japan
III-9-6	State of nationality	JP
III-9-7	State of residence	JP

PCT REQUEST

III-10	**Applicant and/or inventor**	
III-10-1	This person is	applicant and inventor
III-10-2	Applicant for	US only
III-10-4	Name (LAST, First)	ITO, Takashi
III-10-5	Address	c/o Central Pharmaceutical Research Institute of Japan Tobacco Inc., 1-1, Murasaki-cho, Takatsuki-shi, Osaka 5691125 Japan
III-10-6	State of nationality	JP
III-10-7	State of residence	JP
IV-1	**Agent or common representative; or address for correspondence**	
	The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	TAKASHIMA, Hajime
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IV-1-3	Telephone No.	06-6227-1156
IV-1-4	Facsimile No.	06-6227-0260
IV-1-5	e-mail	takatony@nifty.com
IV-1-6	Agent's registration No.	100080791
V	**DESIGNATIONS**	
V-1	**The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.**	
VI-1	**Priority claim of earlier national application**	
VI-1-1	Filing date	08 June 2005 (08.06.2005)
VI-1-2	Number	2005-168901
VI-1-3	Country	JP
VI-2	**Priority claim of earlier national application**	
VI-2-1	Filing date	17 June 2005 (17.06.2005)
VI-2-2	Number	60/692,039
VI-2-3	Country	US

PCT REQUEST

VI-3	**Priority claim of earlier national application**	
VI-3-1	Filing date	03 February 2006 (03.02.2006)
VI-3-2	Number	2006-027097
VI-3-3	Country	JP
VI-4	**Priority claim of earlier national application**	
VI-4-1	Filing date	13 February 2006 (13.02.2006)
VI-4-2	Number	60/772,734
VI-4-3	Country	US
VI-5	**Priority claim of earlier national application**	
VI-5-1	Filing date	17 May 2006 (17.05.2006)
VI-5-2	Number	2006-138252
VI-5-3	Country	JP
VI-6	**Priority document request**	
	The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-3, VI-5
VI-7	**Incorporation by reference :**	
	where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.	
VII-1	**International Searching Authority Chosen**	Japan Patent Office (ISA/JP)

PCT REQUEST

VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	**Check list**	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	9	✓
IX-2	Description	347	-
IX-3	Claims	79	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	436	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-11	Copy of general power of attorney	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	**Figure of the drawings which should accompany the abstract**		
IX-20	**Language of filing of the international application**	Japanese	
X-1	**Signature of applicant, agent or common representative**		
X-1-1	Name (LAST, First)	TAKASHIMA, Hajime (seal)	
X-1-2	Name of signatory		
X-1-3	Capacity		

PCT REQUEST

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/JP
10-6	**Transmittal of search copy delayed until search fee is paid**	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2006/311975

A. CLASSIFICATION OF SUBJECT MATTER
C07D401/14(2006.01), ***A61K31/454***(2006.01), ***A61K31/4545***(2006.01), ***A61K31/506***(2006.01), ***A61K45/00***(2006.01), ***A61P3/04***(2006.01), ***A61P3/06***(2006.01), ***A61P3/10***(2006.01), ***A61P9/12***(2006.01), ***A61P43/00***(2006.01),
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)
A61K31/454, A61K31/4545, A61K31/506, A61K45/00, A61P3/04, A61P3/06, A61P3/10, A61P9/12, A61P43/00, C07D401/14, C07D409/14, C07D417/14, C07C205/23, C07D207/277, C07D207/26, C07D207/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Jitsuyo Shinan Toroku Koho 1996-2006
Kokai Jitsuyo Shinan Koho 1971-2006 Toroku Jitsuyo Shinan Koho 1994-2006

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAplus(STN), REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/089470 A2 (NOVO NORDISK A/S), 21 October, 2004 (21.10.04), Abstract; Claims 46 to 57, 115 to 126; pages 76 to 84 & EP 1615698 A2	1-16,20-33, 35
X	WO 2004/089415 A2 (NOVO NORDISK A/S), 21 October, 2004 (21.10.04), Abstract; Claims 10 to 12, 38 to 55; pages 159 to 167 & EP 1615667 A2	1-16,20-33, 35

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent 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
06 July, 2006 (06.07.06)	18 July, 2006 (18.07.06)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2006/311975

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to clai
A	GB 1513742 A (IMPERIAL CHEMICAL INDUSTRIES LTD.), 07 June, 1978 (07.06.78), Examples 4, 9, 11 & DE 2603399 A & BE 838128 A & NL 7600968 A & NO 7600314 A & SE 7600945 A & JP 51-101992 A & DK 7600322 A & FI 7600236 A & FR 2299029 A & PT 64748 A & ZA 7600414 A & US 4046898 A & AT 7602234 A & AT 7600651 A & US 4126685 A & IL 48938 A & CA 1076580 A & CH 617701 A & CH 618438 A & CH 618439 A & AT 7802233 A & AT 7802235 A & AT 7802236 A & JP 87021794 B & IT 1158736 B	37-44

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2006/311975

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- [x] Claims Nos.: 17-19, 34, 36
  because they relate to subject matter not required to be searched by this Authority, namely:
  Claims 17 to 19, 34 and 36 pertain to [methods for treatment of the human body by therapy] and thus relate to a subject matter which this International Searching Authority is not required, under the provisions of the PCT Rule 39.1(iv), to search.
- [ ] Claims Nos.:
  because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
- [ ] Claims Nos.:
  because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
- [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
- [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
- [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The

- [ ] The additional search fees were accompanied by the applicant's protest and, where applicable, payment of a protest fee..
- [ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- [ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2006/311975

Continuation of A. CLASSIFICATION OF SUBJECT MATTER
(International Patent Classification (IPC))

C07D409/14(2006.01), ***C07D417/14***(2006.01), ***C07C205/53***(2006.01),
C07D207/277(2006.01), ***C07D207/26***(2006.01), ***C07D207/08***(2006.01)

(According to International Patent Classification (IPC) or to both national classification and IPC)

240

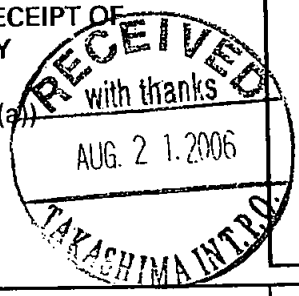
PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))



To:

TAKASHIMA, Hajime
Meiji Yasuda Seimei Osaka Midosuji Bldg., 1-1, Fushimimachi 4-chome,
Chuo-ku, Osaka-shi, Osaka
5410044
Japan

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
04 August 2006 (04.08.2006)	
Applicant's or agent's file reference	**International application No.**
09934	PCT/JP2006/311975

The applicant is hereby **notified** that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

JAPAN TOBACCO INC. (for all designated States except US)
YAMAMOTO, Hiroshi et al (for US)

International filing date	:	08 June 2006 (08.06.2006)
Priority date(s) claimed	:	08 June 2005 (08.06.2005)
		17 June 2005 (17.06.2005)
		03 February 2006 (03.02.2006)
		13 February 2006 (13.02.2006)
		17 May 2006 (17.05.2006)
Date of receipt of the record copy by the International Bureau	:	29 June 2006 (29.06.2006)
List of designated Offices	:	

AP :BW,GH,GM,KE,LS,MW,MZ,NA,SD,SL,SZ,TZ,UG,ZM,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,HU,IE,IS,IT,LT,LU,LV,MC,NL,PL,PT,RO,SE,SI,SK,TR
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
National :AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BW,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EC,EE,EG,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KM,KN,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,LY,MA,MD,MG,MK,MN,MW,MX,MZ,NA,NG,NI,NO,NZ,OM,PG,PH,PL,PT,RO,RU,SC,SD,SE,SG,SK,SL,SM,SY,TJ,TM,TN,TR,TT,TZ,UA,UG,US,UZ,VC,VN,YU,ZA,ZM,ZW

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.70.10

Authorized officer:

Françoise HENNEQUIN (Fax 338 7

Telephone No. (41-22) 338 9935

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Continuation of Form PCT/IB/301

NOTIFICATION OF RECEIPT OF RECORD COPY

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
04 August 2006 (04.08.2006)	
Applicant's or agent's file reference	**International application No.**
09934	PCT/JP2006/311975

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- time limits for entry into the national phase - **see updated important information (as of April 2002)**
- requirements regarding priority documents (if applicable)

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the **"national phase" must be entered** before each of the designated Offices indicated on the cover sheet of this Notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 39 and the applicable national laws. In addition, the applicant may also have to comply **with other special requirements** applicable in certain Offices. It is the **applicant's responsibility** to ensure the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The **applicable time limit** for entering the national phase will, **subject to what is said in the following paragraph,** be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date (see Article 39(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, **time limits other than the 30-month time limit will continue to apply, for various periods of time,** in respect of certain designated or elected Offices. For **regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit),** Office by Office, refer to the PCT Gazette("Section IV" part published on a weekly basis), to the PCT Newsletter (on a monthly basis) and to the relevant National Chapters in Volume II of the PCT Applicant's Guide (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages the site including those of the Gazette, Newsletter and Guide, at http://www.wipo.int/pct/en/index.html.

Information about the requirements for **filing a demand for international preliminary examination** is set out in the PCT Applicant's Guide, Volume I/A, Chapter IX. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within the time limit which is reasonable under the circumstances (Rule 17.1(c)).

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit (and all other PCT time limits) is the filing date of the earliest application whose priority is claimed (Article 2(xi)(b)).

...IVED
...thanks
...- 7. 2006
...ISHIMA INT'L O.

PATENT COOPERATION TREATY

PCT/JP2006/311975

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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

TAKASHIMA, Hajime
Meiji Yasuda Seimei Osaka Midosuji Bldg., 1-1,
Fushimimachi 4-chome, Chuo-ku, Osaka-shi, Osaka
5410044
JAPON

mailing *(day/month/year)* October 2006 (20.10.2006)	
t's or agent's file reference 934	**IMPORTANT NOTIFICATION**
onal application No. CT/JP2006/311975	International filing date *(day/month/year)* 08 June 2006 (08.06.2006)
onal publication date *(day/month/year)* t yet published	Priority date *(day/month/year)* 08 June 2005 (08.06.2005)

nt
JAPAN TOBACCO INC. et al

y means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority ocuments, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to ll earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an sterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau n compliance with Rule 17.1(a) or (b).

f applicable) The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of his Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the riority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to ubmit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 7.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an pportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the ircumstances.

*f applicable)***An asterisk (*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted r transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received fter the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the eceiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in ompliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated)ffices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) rovides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry nto the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No	Country or regional Office or PCT receiving Office	Date of receipt of priority document
3 June 2005 (08.06.2005)	2005-168901	JP	13 July 2006 (13.07.2006)
7 June 2005 (17.06.2005)	60/692,039	US	08 September 2006 (08.09.2006)
February 2006 (03.02.2006)	2006-027097	JP	13 July 2006 (13.07.2006)
February 2006 (13.02.2006)	60/772,734	US	08 September 2006 (08.09.2006)
7 May 2006 (17.05.2006)	2006-138252	JP	13 July 2006 (13.07.2006)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

le No. +41 22 338 82 70

Authorized officer
Masashi Honda

Facsimile No. +41 22 338 70 10
Telephone No. +41 22 338 82 54

From the INTERNATIONAL BUREAU

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PCT

FIRST NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION (TO DESIGNATED OFFICES WHICH DO NOT APPLY THE 30 MONTH TIME LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

TAKASHIMA, Hajime
Meiji Yasuda Seimei Osaka Midosuji Bldg., 1-1, Fushimimachi 4-chome, Chuo-ku, Osaka-shi, Osaka
5410044
JAPON



Date of mailing *(day/month/year)* 11 January 2007 (11.01.2007)	
Applicant's or agent's file reference 09934	IMPORTANT NOTICE

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2006/311975	08 June 2006 (08.06.2006)	08 June 2005 (08.06.2005)

Applicant: JAPAN TOBACCO INC. et al

1. **ATTENTION**: For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does apply**, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93*bis*.1. The International Bureau has effected that communication on the date indicated below:
14 December 2006 (14.12.2006)

   CH

   In accordance with Rule 47.1(c-*bis*)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93*bis*.1 :

   LU, SE, TZ, UG

   In accordance with Rule 47.1(c-*bis*)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. **TIME LIMITS for entry into the national phase**

   For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of **19 months** from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph,** be **20 MONTHS** from the priority date.

   In practice, **time limits other than the 20-month time limit** will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For **regular updates on the applicable time limits** (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

   It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Masashi Honda

e-mail: pt08@wipo.int

From the INTERNATIONAL BUREAU

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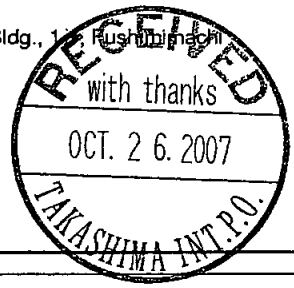
PCT

SECOND AND SUPPLEMENTARY NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION (TO DESIGNATED OFFICES WHICH APPLY THE 30 MONTH TIME LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

TAKASHIMA, Hajime
Meiji Yasuda Seimei Osaka Midosuji Bldg., 1-8, Fushimimachi 4-chome, Chuo-ku, Osaka-shi, Osaka
5410044
JAPON



Date of mailing *(day/month/year)* 11 October 2007 (11.10.2007)	
Applicant's or agent's file reference 09934	**IMPORTANT NOTICE**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2006/311975	08 June 2006 (08.06.2006)	08 June 2005 (08.06.2005)

Applicant: JAPAN TOBACCO INC. et al

1. **ATTENTION**: For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does not apply**, please see Form PCT/IB/308(First Notice) issued previously.

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93*bis*.1. The International Bureau has effected that communication on the date indicated below:
14 December 2006 (14.12.2006)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MZ, NA, NG, PG, RU, SY, TM, US

In accordance with Rule 47.1(c-*bis*)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93*bis*.1 :

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KM, KN, KZ, LC, LK, LR, LS, LT, LV, LY, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, SM, TJ, TN, TR, TT, UA, UZ, VC, VN, YU, ZA, ZM, ZW

In accordance with Rule 47.1(c-*bis*)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. **TIME LIMITS for entry into the national phase**

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph,** be **30 MONTHS** from the priority date.

In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For **regular updates on the applicable time limits** (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Masashi Honda

e-mail: pt08.pct@wipo.int

COMPUESTO HETEROCICLICO

CAMPO TECNICO

La presente invención se refiere a los compuestos heterocíclicos, y más particularmente, a los compuestos heterociclicos útiles como inhibidores de HSD1.

TECNICA ANTERIOR

Según se observa típicamente en el síndrome de Cushing, el efecto del exceso sistémico de glucocorticoides causa anormalidades metabólicas tales como acumulación de grasa visceral, cambios característicos en la distribución de grasa en el cuerpo, resistencia a insulina, diabetes, hiperlipidemia, elevación de la presión arterial y lo similar.

Ha sido conocido durante más de la mitad de un siglo que el glucocorticoide juega a un papel importante en la diabetes y, por ejemplo, la remoción de la hipófisis o la glándula suprarrenal de los animales diabéticos resulta en el alivio de la mayoría de las condiciones greves de diabetes y disminuye la concentración de glucosa en sangre (ver de Long, C.D. y F.D.W. Leukins (1936), "J. Exp. Med." 63: 465-490 y Houssay, B.A. (1942), "Endocrinology", 30,: 884-892).

El glucocorticoide es conocido por (1) ser esencial para el programa de diferenciación e inhibición de adipocito, como una hormona representativa antagónica a insulina, glucosa y metabolismo de lípido por la insulina en varias etapas, (2) aumento de presión arterial vía inducción de producción de sustrato de renina, el cual

es angiotensinógeno, mejora del receptor de expresión de angiotensina II y lo similar, (3) causar hiperorexia y obesidad como una hormona antagónica a leptina potente y lo similar (ver "Rinshoi", vol. 30 No. 9, 2004; 1782-1787).

Adicionalmene, ha estado atrayendo la atención que el efecto de los glucocorticoides anormalmente activados en el tejido adiposo está involucrado en la patología del síndrome metabólico que abarca enfermedades metabólicas múltiples tales como hiperlipidemia de la diabetes, hipertensión, hígado graso y lo similar en un solo individuo (ver de Moller DE. Nuevos objetivos de fármaco para diabetes 2 y síndrome metabólico, "Nature" 2001; 414: 821-7).

Estos hechos sugieren que la reducción del efecto del glucocorticoide sea beneficiosa para el tratamiento o profilaxis de enfermedades metabólicas tales como diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión, hígado graso y lo similar y el síndrome metabólico que abarca las enfermedades metabólicas en un solo individuo, y además, eventos vasculares fatales representados por el infarto cardíaco y la apoplejía cerebral basadas en estas enfermedades.

El glucocorticoide activo (cortisol en el ser humano y corticoesterona en los roedores) que exhibe el efecto del glucocorticoide es producido de cortisona o 11-deshidrocorticoesterona siendo ambos 11-cetometabolitos inactivos por la acción de una enzima de conversión, deshidrogenasa 11β-hidroxiesteroide tipo 1 (11βHSD1), no sólo en glándula suprarrenal sino también los diversos tejidos y células (ver Agurwal y col., "J. Biol. Chem" 264, 18939-46, 1989). Debido a que al ratón al que se administra 11βHSD1 no puede convertir un glucocorticoide inactivo administrado a uno del tipo activo, se ha demostrado que esta enzima puede ser la única enzima que convierte el glucocorticoide al activo en el ser vivo (ver de

Kotelevtsev, y. y col.: "Proc. Natl. Acad. Sci." E.U.A., 94,: 14924, 1997). Hay un informe en un caso de enfermedad de Cushing de hipófisis con hiperglucocorticoidemia en donde no se observaron las condiciones del síndrome de Cushing debido a una actividad de 11βHSD1 notablemente inferior por casualidad (ver de Tomlinson, JW y col.: "J. Clin. Endocrinol. Metab.", 87: 57, 2002).

Estos resultados revelan que la regulación de la actividad de 11βHSD1 es significativa para la acción del glucocorticoide. En otras palabras, la regulación de la actividad de 11βHSD1 es beneficiosa para el tratamiento o profilaxis de enfermedades metabólicas tales como diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión, hígado graso y lo similar y el síndrome metabólico que abarca las enfermedades metabólicas en un solo individuo, y además, eventos vasculares fatales representados por el infarto cardíaco y la apoplejía cerebral basadas en estas enfermedades.

Se ha aclarado que el ratón transgénico, que exhibe sobreexpresión de 11βHSD1, del mismo nivel como el de los individuos obesos, sólo en el tejido adiposo, también tiene los factores principales de síndromes metabólicos tales como obesidad del tipo grasa visceral, diabetes resistente a insulina, hiperlipidemia, hipertensión, hígado graso y lo similar (ver de Masuzaki, H y col.: "Science" 2001; 294: 2166-70 y Masuzaki H y col.: "J. Clin. Invest" 2003; 112: 83-90). Adicionalmene, mientras el ratón transgénico que exhibe sobreexpresión de 11βHSD1 específico del hígado no demuestra un fenotipo de obesidad del tipo grasa visceral pero demuestra resistencia a insulina y patología de hipertensión, hígado graso y lo similar (ver Janice M. Paterson y col.: "PNAS 2004"; 101: 7088-7093). En contraste, al ratón con gen anulado para 11βHSD1 demuestra resistencia a la inducción de enzima de gluconeogénesis hepática (PEPCK, G6Pase etc.) debido a la carga de tensiones o

dieta cargada de alta cantidad de grasa, y demuestra clara resistencia al embate de diabetes (ver Kotelevtsev, Y. y col.: "Proc. Natl. Acad. Sci." E.U.A., 94,: 14924, 1997).

Además, el ratón con gen anulado para 11βHSD1 demuestra disminución en el nivel del triglicérido en sangre e incremento de nivel de HDL-colesterol en sangre, porque las expresiones de grupo molecular relacionadas al catabolismo de grasa y su factor de coordinación de transcripción PPARα aumenta notablemente. Se ha informado que el ratón con gen anulado para 11βHSD1 demuestra una evidente atenuación de la acumulación de tejido adiposo visceral y ataque de anormalidades metabólicas inducidas por la dieta cargada de alta cantidad de grasa (ver Morton NM y col. "J. Biol. Chem." 2001; 44: 41293-301).

En realidad, debido a que la sensibilidad a insulina se incrementa con la deficiencia de 11βHSD1, se espera que la inhibición del efecto de esta enzima sea útil para el tratamiento o profilaxis de la diabetes no dependiente de insulina y obesidad (ver de Seckl, JR y col. "Eur. J. Biochem." 249: 361, 1997 y de Morton NM y col. "Diabetes" 2004; 53: 931-938).

Estos halllazgos afirman que la reducción del efecto de 11βHSD1 es beneficiosa para el tratamiento o profilaxis de enfermedades metabólicas tales como diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión, hígado graso y lo similar y síndrome metabólico que abarca las enfermedades metabólicas en un solo individuo, y además, eventos vasculares fatales representados por infarto cardiaco y apoplejía cerebral basadas en esas enfermedades.

La remoción de la glándula suprarrenal debilita el efecto de ayuno lo cual incrementa la ingesta de comida y expresión de neuropéptido hipotalámico Y. Esto apoya el papel del glucocorticoide en el aumento de ingesta de comida y sugiere

que la inhibición de 11βHSD1 en el cerebro aumentará el nivel de saciedad, y por consiguiente, disminuye la ingesta de comida (ver de Woods, S.C. y col. (1998) "Science", 280:1378-1383). Es decir, se sugiere que la reducción del efecto de 11βHSD1 sea beneficiosa para el tratamiento o profilaxis de hiperorexia.

Las tensiones nerviosas y los glucocorticoides afectan la función cognoscitiva (ver de Quervain, D.J. -F., B. Roozendaal, y J.L. McGaugh (1998), "Nature", 394,: 787-790). En realidad, el ratón con gen anulado para 11βHSD1 demuestra una marcada mejora en el trastorno cognoscitivo causado por envejecimiento (ver Yau J L y col. "PNAS 2001"; 98: 4716-4721)., y un reciente informe ha documentado que un inhibidor de 11βHSD1 no específico, carbenoxolona, es eficaz para el trastorno cognoscitivo del ser humano anciano (ver Sandeep T C y col. PNAS 2004; 101: 6734-6739). Además, la 11βHSD1 controla el nivel de acción de glucocorticoide en el cerebro, contribuyendo por esto a la neurotoxicidad (ver Rajan, V., C.R.W. Edwards, y J.R. Seckl, J. (1996), "Neuroscience", 16:65-70 y de Seckl, J.R., "Front. (2000), Neuroendocrinol", 18:49-99). Además, la inhibición de 11βHSD1 en el cerebro resulta en la reducción de la ansiedad, lo cual está basado en el efecto indicado precedentemente y conocido del glucocorticoide en el cerebro (ver Tronche, F. y col. (1999), "Nature Genetics", 23:99-103). En conjunto, por consiguiente, los mismos sugieren que la reducción del efecto de 11βHSD1 en el cerebro humano prevenga la reactivación de cortisona al cortisol, y es útil para el tratamiento o profilaxis de disgnosia, enfermedades neurodegenerativas acompañadas por desaparición de células nerviosas, desórdenes emocionales tales como ansiedad, depresión, manía y lo similar, esquizofrenia, neurodisfunción que incluye el estímulo del apetito y lo similar.

Es un hecho muy conocido que el glucocorticoide suprime el sistema

inmunológico. Por consiguiente, se sugiere que la reducción del efecto de 11βHSD1 sea beneficiosa para el tratamiento o profilaxis de enfermedades que demuestran una inmunidad disminuída tal como inmunodeficiencia y lo similar o para el tratamiento o profilaxis de enfermedades que requieren un aumento de inmunidad.

Los recientes datos sugieren que los niveles de receptor de glucocorticoide objetivo y enzima 11βHSD1 determinan la susceptibilidad al glaucoma (ver de Stokes, J. y col. (2000), "Invest. Ophthalmol." 41: 1629-1638). Por lo tanto, se sugiere que la reducción del efecto de 11βHSD1 sea beneficiosa para el tratamiento o profilaxis de glaucoma.

Aunque el glucocorticoide juega una parte esencial en el crecimiento y función del esqueleto, el glucocorticoide en exceso es perjudicial. La pérdida de hueso inducida por glucocorticoide es por lo menos parcialmente inducida por medio de la inhibición de la formación del hueso inclusive la supresión de crecimiento de osteoblasto y síntesis de colágeno (ver de Kim, C.H., S.L. Cheng, y G.S. Kim (1999), "J. Endocrinol", 162,: 371-379).

El efecto negativo en la formación del nódulo de hueso puede ser bloqueado por un inhibidor de 11βHSD1 no específico, carbenoxolona lo cual hace pensar en un papel importante del 11βHSD1 en el efecto de glucocorticoide (ver de Bellows, C.G., A. Ciaccia, y J.N.M. Heersche, (1998), "Bone", 23: 119-125). Por consiguiente, la reducción del efecto del 11βHSD1 se sugiere que sea beneficiosa para el tratamiento o profilaxis de osteoporosis.

Concordantemente, puede decirse que una substancia que posea una actividad que reduzca el efecto de 11βHSD1 es útil como fármaco para el tratamiento o profilaxis de la patología que involucra al glucocorticoide, tal como

1) las enfermedades metabólicas que incluyen diabetes, resistencia a

insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión e hígado graso,

2) el síndrome metabólico,

3) eventos vasculares fatales representados por el infarto cardíaco y la apoplejía cerebral basadas en tales enfermedades,

4) el hiperorexia,

5) las enfermedades que incluyen disgnosia, enfermedades neurodegenerativas acompañadas por la desaparición de células nerviosas, desórdenes emocionales tales como ansiedad, depresión, manía y lo similar, esquizofrenia y neurodisfunción inclusive el estímulo del apetito,

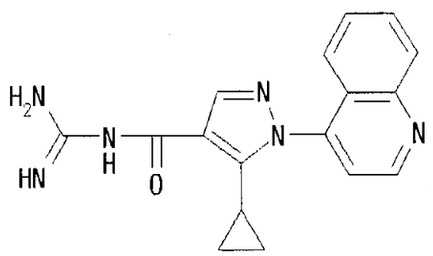
6) enfermedades que requieren tratamiento o profilaxis de inmunidad disminuída o aumento de inmunidad, tal como la inmunodeficiencia y lo similar,

7) glaucoma,

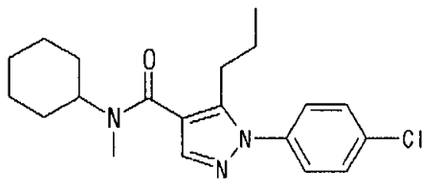
8) osteoporosis

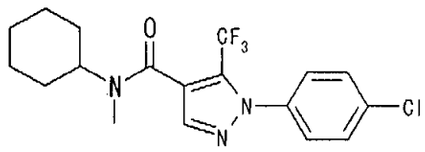
y lo similar.

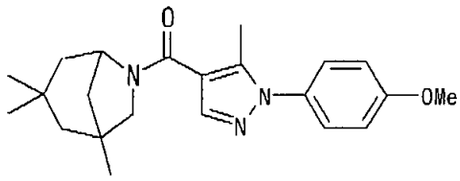
Como compuesto heterocíclico, por ejemplo, es conocido lo siguiente. Por ejemplo, la WO99/43663 describe los siguientes compuestos heterocíclicos como un compuesto que posee acción inhibitoria de NHE1.



Como los inhibidores de 11βHSD1 conocidos, por ejemplo, se puede indicar lo siguiente. La WO2004/089470 describe los compuestos siguientes como compuestos que tienen una acción inhibitoria en 11βHSD1:







DESCRIPCION DE LA INVENCION

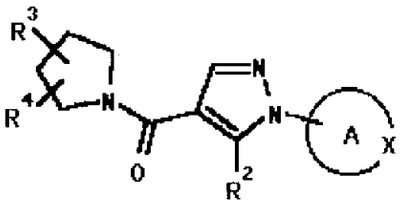
Hay una fuerte demanda para el desarrollo de un compuesto útil como un agente para la profiláctica o tratamiento de enfermedades metabólicas tales como diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión, hígado graso y lo similar, y lo similar, que tenga propiedades más superiores como producto farmacéutico en lo que se refiere a la eficacia, duración de acción, especificidad, baja toxicidad, absorbabilidad oral, farmacocinética y lo similar.

Es por consiguiente un objeto de la presente invención proveer un compuesto que posee una acción inhibitoria de HSD1 y lo similar y sea útil como agente para profilaxis o tratamiento de enfermedades metabólicas tales como diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión, hígado graso y lo similar, que posea una estructura química diferente de

la de los compuestos conocidos inclusive los compuestos mencionados y el uso de los mismos.

Los presentes inventores han encontrado primero que un compuesto heterocíclico mencionado más adelante posee una acción inhibitoria de HSD1 superior, y es útil como un agente para profilaxis o tratamiento de enfermedades metabólicas tales como diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión, hígado graso y lo similar. Los presentes inventores han realizado estudios intensivos basados en estos resultados y han completado la presente invención. Concordantemente, la presente invención provee específicamente lo siguiente.

1. Un compuesto representado por la fórmula siguiente [1'].:



[1']

en donde

el anillo A es

(1) un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o

(2) un grupo cicloalquilo,

dicho anillo A es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes R^1,

dicho sustituyente R^1 es

1) un átomo de hidrógeno,

2) $-CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es

(a) un átomo de hidrógeno,

(b) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo carboxilo,

d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y.

e) un grupo alcoxilo de C_{1-6}),

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(c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})).

(d) un grupo alquilo de C_{1-6} ,dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo.

b) un átomo de halógeno,

c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)).

d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, ó R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterociclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv):

(i) un átomo de halógeno.

(ii) un grupo hidroxilo,

(iii) un grupo oxo, y

(iv) un grupo alcoxilo de C_{1-6}),

e) un grupo alcoxilo de C_{1-6}, y

f) un grupo carboxilo).

(e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}.

(f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y.

c) un grupo oxo),

(g) un grupo alcoxilo de C_{1-6}, o

(h) un grupo heterocíclico monocíclico no saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes).

, o

(i) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o un grupo heterocíclico que es un anillo fusionado de dicho heterociclo y un anillo de carbono (ambos grupos heterocíclicos mencionados son opcionalmente sustituidos con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}),

d) un grupo carboxilo,

e) un grupo -CO-alquilo de C_{1-6}

f) $-CO-NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

g) un grupo oxo,

h) $-NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

i) un grupo alcoxilo de C_{1-6})

3) $-COOR^{10}$ en donde R^{10} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al d):

a) un grupo hidroxilo,

b) $-NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

c) un grupo alcoxilo de C_{1-6}, y

d) un grupo arilo), o

(b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

4) $-COR^{11}$ en donde R^{11} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al h):

a) un átomo de halógeno.

b) un grupo hidroxilo,

c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

d) $-CO-NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

e) un grupo alcoxilo de C_{1-6},

f) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con

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uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo alcoxilo de C_{1-6}, y (iv) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

g) un grupo carboxilo, y.

h) un grupo ariloxilo),

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b):

a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y.

b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})),

(c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

(d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con

uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) a (3): (1) un átomo de halógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), y (3) un grupo alcoxilo de C_{1-6}), o

(e) un grupo carboxilo,

5) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (d):

(un) un grupo carboxilo.

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno),

(c)-CO-$NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

(d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes))),

6) un grupo cicloalquilo,

7) -$S(=O)_2$-R^{12} en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

8) -C(=NCN)-R^{13} en donde R^{13} es un grupo alquilo de C_{1-6},

9) -C(=NCN)$NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

10) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) al (f):

(a) un grupo carboxilo,

(b) un átomo de halógeno,

(c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, y c) un grupo alcoxilo de C_{1-6}),

(d) -$NR^{38}R^{39}$ en donde R^{38} y R^{39} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, -CO-$NR^{40}R^{41}$ en donde R^{40} y R^{41} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo alcoxilo de C_{1-6}, o R^{40} y R^{41} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo

heterocíclico monocíclico saturado que contiene nitrógeno, ó -$S(=O)_2$-R^{42} en donde R^{42} es un grupo alquilo de C_{1-6}, o R^{38} y R^{39} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más grupos oxo),

(e) -CO-$NR^{43}R^{44}$ en donde R^{43} y R^{44} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{43} y R^{44} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

(f) un grupo -COO-alquilo de C_{1-6}), o

11) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (h):

(a) un grupo carboxilo,

(b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un átomo de halógeno,

b) un grupo hidroxilo, y

c) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo,

(d) un átomo de halógeno,

(e) -CO-$NR^{45}R^{46}$ en donde R^{45} y R^{46} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{45} y R^{46} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico

monocíclico saturado que contiene nitrógeno,

(f) un grupo -COO-alquilo de C_{1-6},

(g) un grupo ciano, y

(h) un grupo alcoxilo de C_{1-6});

-X- es

(1) $-N(R^1)-$ en donde R^1 es igual al definido anteriormente, o

(2) $-C(R^7R^8)-$ en donde R^7 y R^8 son iguales o diferentes y cada uno es

1) un átomo de hidrógeno,

2) $-NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o $-CO-NR^{36}R^{37}$ en donde R^{36} y R^{37} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{36} y R^{37} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o R^{16} y R^{17} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

3) $-CONR^{18}R^{19}$ en donde R^{18} y R^{19} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más grupos carboxilo), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un átomo de halógeno, y (b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o R^{18} y R^{19} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno.

4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó 6

miembros, o

5) un grupo carboxilo;

R^2 es

(1) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un grupo hidroxilo, y (b) un grupo alcoxilo de C_{1-6}), y 2) un grupo alcoxilo de C_{1-6}); y

R^3 y R^4 son iguales o diferentes y cada uno es

(1) un átomo de hidrógeno,

(2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un átomo de halógeno, 2) un grupo hidroxilo, 3) un grupo alcoxilo de C_{1-6}, y 4) es un grupo -OCO-alquilo de C_{1-6}),

(3) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente 1) a 6): .

1) un átomo de halógeno,

2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un átomo de halógeno, (b) un grupo hidroxilo, y (c) un grupo alcoxilo de C_{1-6}),

3) un grupo alcoxilo de C_{1-6} (dicho grupo alcoxilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes).

4) un grupo carboxilo,

5) un grupo -COO-alquilo de C_{1-6}, y

6) un grupo ciano),

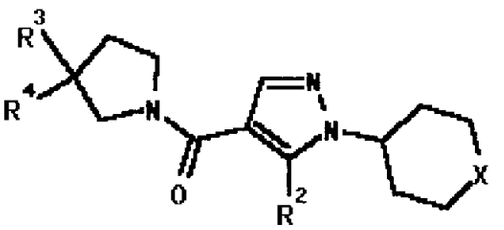
(4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un átomo de halógeno, y 2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

(5) un grupo hidroxilo, o

(6) un grupo alcoxilo de C_{1-6}],

o una sal del mismo.

2. Un compuesto representado por la fórmula siguiente [1]:



[1]

en donde

-X- es

(1) -N(R^1)- en donde R^1 es

1) un átomo de hidrógeno,

2) -CONR^{5}R^6 en donde R^5 y R^6 son iguales o diferentes y cada uno es

(a) un átomo de hidrógeno,

(b) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo carboxilo,

d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y.

e) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})),

(d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o

diferentes seleccionados de lo siguiente (i) a (iv):

(i) un átomo de halógeno,

(ii) un grupo hidroxilo,

(iii) un grupo oxo, y

(iv) un grupo alcoxilo de C_{1-6}),

e) un grupo alcoxilo de C_{1-6}, y

f) un grupo carboxilo),

(e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6},

(f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

(g) un grupo alcoxilo de C_{1-6}, o

(h) un grupo heterocíclico monocíclico no saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes),

o.

(i) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene

nitrógeno, o un grupo heterocíclico que es un anillo fusionado de dicho heterociclo y un anillo de carbono (ambos grupos heterocíclicos mencionados son sustituidos opcionalmente con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}),

d) un grupo carboxilo,

e) un grupo -CO-alquilo de C_{1-6},

f) $-CO-NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

g) un grupo oxo,

h) $-NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

i) un grupo alcoxilo de C_{1-6}),

3) $-COOR^{10}$ en donde R^{10} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes

seleccionados de los siguientes a) al d):

a) un grupo hidroxilo,

b) $-NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

c) un grupo alcoxilo de C_{1-6}, y

d) un grupo arilo), o

(b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

4) $-COR^{11}$ en donde R^{11} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al h):

a) un átomo de halógeno,

b) un grupo hidroxilo.

c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

d) -CO-$NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

e) un grupo alcoxilo de C_{1-6},

f) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo alcoxilo de C_{1-6}, y (iv) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

g) un grupo carboxilo, y

h) un grupo ariloxilo),

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b):

a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y

b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})),

(c) un grupo heterocíclico monocíclico saturado que contiene

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nitrógeno (dicho grupo heterociclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

(d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) a (3): (1) un átomo de halógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), y (3) un grupo alcoxilo de C_{1-6}), o

(e) un grupo carboxilo,

5) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (d):

(a) un grupo carboxilo

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno),

(c) -CO-$NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente

forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

(d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes))),

6) un grupo cicloalquilo,

7) $-S(=O)_2-R^{12}$ en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

8) $-C(=NCN)-R^{13}$ en donde R^{13} es un grupo alquilo de C_{1-6},

9) $-C(=NCN)NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

10) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (f):

(a) un grupo carboxilo,

(b) un átomo de halógeno,

(c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, y

c) un grupo alcoxilo de C_{1-6}),

(d) $-NR^{38}R^{39}$ en donde R^{38} y R^{39} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, $-CO-NR^{40}R^{41}$ en donde R^{40} y R^{41} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo alcoxilo de C_{1-6}, o R^{40} y R^{41} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o $-S(=O)_2-R^{42}$ en donde R^{42} es un grupo alquilo de C_{1-6}, o R^{38} y R^{39} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más grupos oxo)),

(e) $-CO-NR^{43}R^{44}$ en donde R^{43} y R^{44} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{43} y R^{44} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

(f) un grupo -COO-alquilo de C_{1-6}), o

11) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (h):

(a) un grupo carboxilo,

(b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un átomo de halógeno,

b) un grupo hidroxilo, y

c) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo,

(d) un átomo de halógeno,

(e) -CO-$NR^{45}R^{46}$ en donde R^{45} y R^{46} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{45} y R^{46} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

(f) un grupo -COO-alquilo de C_{1-6},

(g) un grupo ciano, y

(h) un grupo alcoxilo de C_{1-6}), o

(2) -C(R^7R^8)- en donde R^7 y R^8 son iguales o diferentes y cada uno es

1) un átomo de hidrógeno,

2) -$NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o -CO-$NR^{36}R^{37}$ en donde R^{36} y R^{37} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{36} y R^{37} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, ó R^{16} y R^{17} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

3) -$CONR^{18}R^{19}$ en donde R^{18} y R^{19} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más grupos carboxilo), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un átomo de halógeno, y (b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno

o más átomos halógenos iguales o diferentes)), o R^{18} y R^{19} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros, o

5) un grupo carboxilo;

R^2 es

(1) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un grupo hidroxilo, y (b) un grupo alcoxilo de C_{1-6}), y 2) un grupo alcoxilo de C_{1-6}); y

R^3 y R^4 son iguales o diferentes y cada uno es

(1) un átomo de hidrógeno,

(2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un átomo de halógeno, 2) un grupo hidroxilo, 3) un grupo alcoxilo de C_{1-6}, y 4) un grupo que es -OCO-alquilo de C_{1-6}),

(3) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente 1) a 6):

1) un átomo de halógeno,

2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un átomo de halógeno, (b) un grupo hidroxilo,

y (c) un grupo alcoxilo de C_{1-6}),

3) un grupo alcoxilo de C_{1-6} (dicho grupo alcoxilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes),

4) un grupo carboxilo,

5) un grupo -COO-alquilo de C_{1-6}, y

6) un grupo ciano),

(4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un átomo de halógeno, y 2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

(5) un grupo hidroxilo, o

(6) un grupo alcoxilo de C_{1-6}],

o una sal del mismo.

3. El compuesto de acuerdo con cualquiera de los 1 y 2 indicados precedentemente, en donde el -X- es un -C(R^7R^8)- en donde R^7 y R^8 son iguales a los definidos en el 1 indicado precedentemente, o una sal del mismo.

4. El compuesto de acuerdo con cualquiera de 1 a 3 indicados precedentemente, en donde R^8 es

1) -$NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{16} y R^{17} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno.

2) -$CONR^{18}R^{19}$ en donde R^{18} y R^{19} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{18} y R^{19} opcionalmente

forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o

3) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros,

o una sal del mismo.

5. El compuesto de acuerdo con 1 o 2 indicados precedentemente, en donde -X- es $-N(R^1)-$ en donde R^1 es igual al definido en el 1 indicado precedentemente, o una sal del mismo.

6. El compuesto de acuerdo con cualquiera de 1, 2 y 5 indicados precedentemente, en donde R^1 es

1) un átomo de hidrógeno,

2) $-CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es

(a) un átomo de hidrógeno,

(b) un grupo arilo (dicho grupo arilo se sustituye por uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo carboxilo,

d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}) y

e) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo

alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})),

(d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} se sustituye con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv):

(i) un átomo de halógeno,

(ii) un grupo hidroxilo,

(iii) un grupo oxo, y.

(iv) un grupo alcoxilo de C_{1-6}),

e) un grupo alcoxilo de C_{1-6}, y

f) un grupo carboxilo),

(e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes

seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, o

(f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo), o

(g) un grupo heterocíclico monocíclico no saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes).

o

(h) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i):

a) un átomo de halógeno,

b) un grupo hidroxilo.

c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}),

d) un grupo carboxilo,

e) un grupo -CO-alquilo de C_{1-6},

f) -CO-$NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

g) un grupo oxo,

h) -$NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

i) un grupo alcoxilo de C_{1-6}) (con la condición que R^5 y R^6 no son simultáneamente átomos de hidrógeno),

3) -$COOR^{10}$ en donde R^{10} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al d):

a) un grupo hidroxilo,

b) -$NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

c) un grupo alcoxilo de C_{1-6}, y.

d) un grupo arilo), o

(b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

4) $-COR^{11}$ en donde R^{11} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al h):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

d) $-CO-NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

e) un grupo alcoxilo de C_{1-6}.

f) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo alcoxilo de C_{1-6}, y (iv) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

g) un grupo carboxilo, y

h) un grupo ariloxilo),

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b):

a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y

b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), o

(c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

(d) un grupo arilo (dicho grupo arilo es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) a (3): (1) un átomo de halógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), y (3) un grupo alcoxilo de C_{1-6}), o

(e) un grupo carboxilo,

5) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (d):

(a) un grupo carboxilo,

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno),

(c) -CO-$NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

(d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes))),

6) un grupo cicloalquilo.

7) -$S(=O)_2$-R^{12} en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un

átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

8) $-C(=NCN)-R^{13}$ en donde R^{13} es un grupo alquilo de C_{1-6},

9) $-C(=NCN)NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

10) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (f):

(a) un grupo carboxilo,

(b) un átomo de halógeno,

(c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, y c) un grupo alcoxilo de C_{1-6}),

(d) $-NR^{38}R^{39}$, en donde R^{38} y R^{39} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, $-CO-NR^{40}R^{41}$ en donde R^{40} y R^{41} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo alcoxilo de C_{1-6}, o R^{40} y R^{41} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o $-S(=O)_2-R^{42}$ en donde R^{42} es un grupo alquilo de C_{1-6}), o R^{38} y R^{39} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más grupos oxo).

(e) -CO-$NR^{43}R^{44}$ en donde R^{43} y R^{44} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{43} y R^{44} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

(f) un grupo -COO-alquilo de C_{1-6}), o

11) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (h):

(a) un grupo carboxilo,

(b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un átomo de halógeno,

b) un grupo hidroxilo, y

c) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo, y

(d) un átomo de halógeno,

(e) -CO-$NR^{45}R^{46}$ en donde R^{45} y R^{46} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{45} y R^{46} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

(f) un grupo -COO-alquilo de C_{1-6},

(g) un grupo ciano, y

(h) un grupo alcoxilo de C_{1-6}),

o una sal del mismo.

7. El compuesto de acuerdo con cualquiera de los 1, 2 y 5 indicados precedentemente, en donde R^1 es

1) $-CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es

(a) un átomo de hidrógeno,

(b) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo carboxilo,

d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y

e) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})),

(d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con

uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv):

(i) un átomo de halógeno,

(ii) un grupo hidroxilo,

(iii) un grupo oxo, y

(iv) un grupo alcoxilo de C_{1-6}),

e) un grupo alcoxilo de C_{1-6}, y

f) un grupo carboxilo),

(e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, o

(f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

(g) un grupo alcoxilo de C_{1-6}, o

(h) un grupo heterocíclico monocíclico no saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o

(i) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}),

d) un grupo carboxilo,

e) un grupo -CO-alquilo de C_{1-6},

f) $-CO-NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

g) un grupo oxo,

h) $-NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un

grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

i) un grupo alcoxilo de C_{1-6}) (con la condición que R^5 y R^6 no son cualquier combinación de sustituyentes seleccionada del grupo siguiente: (i) un átomo de hidrógeno, y (ii) un grupo alquilo de C_{1-6} sin sustituir).

2) $-COOR^{10}$ en donde R^{10} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al d):

a) un grupo hidroxilo,

b) $-NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

c) un grupo alcoxilo de C_{1-6}, y

d) un grupo arilo), o

(b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

3) $-COR^{11}$ en donde R^{11} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al h):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

d) $-CO-NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

e) un grupo alcoxilo de C_{1-6},

f) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo alcoxilo de C_{1-6}, y (iv) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

g) un grupo carboxilo, y

h) un grupo ariloxilo),

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b):

a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6}

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es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y

b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), o

(c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

(d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) a (3): (1) un átomo de halógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), y (3) un grupo alcoxilo de C_{1-6}), o

(e) un grupo carboxilo,

4) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (d):

(a) un grupo carboxilo.

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes

iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno),

(c) $-CO-NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

(d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes))),

5) un grupo cicloalquilo.

6) $-S(=O)_2-R^{12}$ en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más átomos halógenos iguales o diferentes), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

7) $-C(=NCN)-R^{13}$ en donde R^{13} es un grupo alquilo de C_{1-6},

8) $-C(=NCN)NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o

9) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de

6 miembros (dicho grupo heterocíclico es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (g):

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un átomo de halógeno,

b) un grupo hidroxilo, y

c) un grupo alcoxilo de C_{1-6}).

(b) un grupo cicloalquilo,

(c) un átomo de halógeno,

(d) -CO-$NR^{45}R^{46}$ en donde R^{45} y R^{46} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{45} y R^{46} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

(e) un grupo -COO-alquilo de C_{1-6},

(f) un grupo ciano, y

(g) un grupo alcoxilo de C_{1-6}),

o una sal del mismo.

8. El compuesto de acuerdo con cualquiera de 1, 2 y 5 indicado precedentemente, en donde R^1 es

1) -$CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es

(a) un átomo de hidrógeno,

(b) un grupo arilo (dicho grupo arilo es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo carboxilo,

d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y

e) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})),

(d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno.

c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o

diferentes seleccionados de lo siguiente (i) a (iv):

(i) un átomo de halógeno,

(ii) un grupo hidroxilo,

(iii) un grupo oxo, y

(iv) un grupo alcoxilo de C_{1-6}).

e) un grupo alcoxilo de C_{1-6}, y

f) un grupo carboxilo),

(e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, o

(f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6}, y

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo), o

(g) un grupo heterocíclico monocíclico no saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o

(h) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}),

d) un grupo carboxilo,

e) un grupo -CO-alquilo de C_{1-6},

f) $-CO-NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

g) un grupo oxo,

h) $-NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

i) un grupo alcoxilo de C_{1-6}) (con la condición que R^5 y R^6 no son simultáneamente átomos de hidrógeno),

2) $-COOR^{10}$ en donde R^{10} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al d):

a) un grupo hidroxilo,

b) $-NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es

un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

c) un grupo alcoxilo de C_{1-6}, y

d) un grupo arilo), o

(b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

3) $-COR^{11}$ en donde R^{11} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al h):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

d) $-CO-NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico

monocíclico saturado que contiene nitrógeno,

e) un grupo alcoxilo de C_{1-6},

f) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo alcoxilo de C_{1-6}, y (iv) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

g) un grupo carboxilo, y

h) un grupo ariloxilo),

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b):

a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y

b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), o

(c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

(d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) a (3): (1) un átomo de halógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), y (3) un grupo alcoxilo de C_{1-6}), o

(e) un grupo carboxilo,

4) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (d):

(a) un grupo carboxilo,

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno),

(c) -CO-$NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

(d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a)

un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes))),

5) un grupo cicloalquilo,

6) $-S(=O)_2-R^{12}$ en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más átomos halógenos iguales o diferentes), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

7) $-C(=NCN)-R^{13}$ en donde R^{13} es un grupo alquilo de C_{1-6},

8) $-C(=NCN)NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o

9) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (g):

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un átomo de halógeno,

b) un grupo hidroxilo, y

c) un grupo alcoxilo de C_{1-6}),

(b) un grupo cicloalquilo,

(c) un átomo de halógeno,

(d) -CO-$NR^{45}R^{46}$ en donde R^{45} y R^{46} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{45} y R^{46} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

(e) un grupo -COO-alquilo de C_{1-6},

(f) un grupo ciano, y

(g) un grupo alcoxilo de C_{1-6}),

o una sal del mismo.

9. El compuesto de acuerdo con cualquiera de 1 a 8 indicado precedentemente, en donde R^2 es un grupo ciclopropilo o es un grupo 1-metilciclopropilo, o una sal del mismo.

10, el compuesto de acuerdo con cualquiera de 1 a 9 indicado precedentemente, en donde R^3 y R^4 son iguales o diferentes y cada uno es

(1) un átomo de hidrógeno,

(2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un átomo de halógeno, y 2) un grupo -OCO-alquilo de C_{1-6}),

(3) un grupo arilo (dicho grupo arilo es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente 1) a 5):

1) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un átomo de halógeno, y (b) un grupo hidroxilo),

2) un grupo alcoxilo de C_{1-6} (dicho grupo alcoxilo de C_{1-6} es sustituido con uno o más átomos halógenos iguales o diferentes),

3) un grupo carboxilo,

4) un grupo -COO-alquilo de C_{1-6}, y

5) un grupo ciano), o

(4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un átomo de halógeno, y 2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

(con la condición que R^3 y R^4 no sean simultáneamente átomos de hidrógeno),

o una sal del mismo.

11. El compuesto del 1 indicado precedentemente, en donde R^1 es

1) $-CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es

(a) un átomo de hidrógeno,

(b) un grupo arilo (dicho grupo arilo es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo carboxilo,

d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y

e) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo

alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})),

(d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv):

(i) un átomo de halógeno,

(ii) un grupo hidroxilo,

(iii) un grupo oxo, y

(iv) un grupo alcoxilo de C_{1-6}),

e) un grupo alcoxilo de C_{1-6}, y

f) un grupo carboxilo),

(e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes

seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, o

(f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

(g) un grupo alcoxilo de C_{1-6}, o

(h) un grupo heterocíclico monocíclico no saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o

(i) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}),

d) un grupo carboxilo,

e) un grupo -CO-alquilo de C_{1-6},

f) -CO-$NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

g) un grupo oxo,

h) -$NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

i) un grupo alcoxilo de C_{1-6}) (con la condición que R^5 y R^6 no sean simultáneamente átomos de hidrógeno),

2) -$COOR^{10}$ en donde R^{10} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al d):

a) un grupo hidroxilo,

b) -$NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

c) un grupo alcoxilo de C_{1-6}, y

d) un grupo arilo), o

(b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo)),

3) $-COR^{11}$ en donde R^{11} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) a la h):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

d) $-CO-NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

e) un grupo alcoxilo de C_{1-6},

f) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo alcoxilo de C_{1-6}, y (iv) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

g) un grupo carboxilo, y

h) un grupo ariloxilo),

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b):

a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y

b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), o

(c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

(d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) a (3): (1) un átomo de halógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), y (3) un grupo alcoxilo de C_{1-6}), o

(e) un grupo carboxilo,

4) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (d):

(a) un grupo carboxilo,

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno),

(c) -CO-$NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

(d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes))),

5) un grupo cicloalquilo,

6) -$S(=O)_2$-R^{12} en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} se sustituye con uno o más átomos halógenos iguales o diferentes), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente

sustituido con uno o más átomos halógenos iguales o diferentes)),

7) -C(=NCN)-R^{13} en donde R^{13} es un grupo alquilo de C_{1-6},

8) -C(=NCN)$NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

9) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (f):

(a) un grupo carboxilo,

(b) un átomo de halógeno,

(c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, y c) un grupo alcoxilo de C_{1-6}),

(d) -$NR^{38}R^{39}$ en donde R^{38} y R^{39} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, -CO-$NR^{40}R^{41}$ en donde R^{40} y R^{41} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo alcoxilo de C_{1-6}, o R^{40} y R^{41} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o -$S(=O)_2$-R^{42} en donde R^{42} es un grupo alquilo de C_{1-6}), o R^{38} y R^{39} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más grupos oxo),

(e) -CO-$NR^{43}R^{44}$ en donde R^{43} y R^{44} son iguales o diferentes y cada

uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{43} y R^{44} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

(f) un grupo -COO-alquilo de C_{1-6}), o

10) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (h):

(a) un grupo carboxilo,

(b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un átomo de halógeno,

b) un grupo hidroxilo, y

c) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo,

(d) un átomo de halógeno,

(e) -CO-$NR^{45}R^{46}$ en donde R^{45} y R^{46} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{45} y R^{46} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

(f) un grupo -COO-alquilo de C_{1-6},

(g) un grupo ciano, y

(h) un grupo alcoxilo de C_{1-6}),

o una sal del mismo.

12. El compuesto del 1 indicado precedentemente, o una sal del

mismo, que se selecciona de lo siguiente:

(1) 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-3-(piridin-3-il)pirrolidina,

(2) clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(3) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(4) 1-[1-(1-carbamoilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(5) 1-{1-[1-(2-carboxifenilcarbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(6) 1-{5-ciclopropil-1-[1-(2-hidroximetilfenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(7) 1-{5-ciclopropil-1-[1-(1-hidroximetilciclopropilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(8) 1-{5-ciclopropil-1-[1-(2-hidroxietilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(9) 1-{5-ciclopropil-1-[1-(2-hidroxi-1,1-dimetiletilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(10) 1-{1-[1-(2-acetilaminoetilcarbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(11) clorhidrato de 1-{1-[1-(2-aminoetilcarbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(12) 1-{5-ciclopropil-1-[1-(1,1-dioxotiomorfolina-4-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(13) clorhidrato de 1-{5-ciclopropil-1-[1-(2-dimetilaminoetil-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(14) 1-{5-ciclopropil-1-[1-(4-hidroxipiperidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(15) 1-{1-[1-(azetidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(16) 1-{5-ciclopropil-1-[1-(3-hidroxipirrolidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(17) 1-{5-ciclopropil-1-[1-(2-piperidin-1-il-etilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(18) 1-{5-ciclopropil-1-[1-(4,4-difluoropiperidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(19) 1-{5-ciclopropil-1-[1-(3,3-difluoropirrolidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(20) 1-{5-ciclopropil-1-[1-(3-hidroxiazetidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(21) 1-(5-ciclopropil-1-{1-[(R)-3-hidroxipirrolidin-1-carbonil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(22) 1-(5-ciclopropil-1-{1-[(S)-3-hidroxipirrolidin-1-carbonil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(23) 1-(5-ciclopropil-1-{1-[(S)-2-hidroxi-1-metiletilcarbamoil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(24) 1-{5-ciclopropil-1-[1-(4-hidroximetilpiperidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(25) 1-{1-[1-(4-carboxipiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-

1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(26) 1-{5-ciclopropil-1-[1-(3-oxopiperazin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(27) 1-(5-ciclopropil-1-{1-[(S)-2-hidroximetilpirrolidin-1-carbonil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(28) 1-{5-ciclopropil-1-[1-(3-hidroximetilazetidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(29) clorhidrato de 1-{5-ciclopropil-1-[1-(4-metilpiperazin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(30) clorhidrato de 1-{5-ciclopropil-1-[1-(4-isopropilpiperazin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(31) 1-{1-[1-(4-acetilpiperazin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(32) 1-(5-ciclopropil-1-{1-[(R)-3-hidroxipiperidin-1-carbonil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(33) 1-{1-[1-(4-carbamoilpiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(34) 1-{1-[1-(3-carbamoilazetidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(35) clorhidrato de 1-{1-[1-(4-aminopiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(36) clorhidrato de 1-{1-[1-(3-aminopirrolidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(37) clorhidrato de 1-{5-ciclopropil-1-[1-(piperidin-4-il-carbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(38) clorhidrato de 1-{5-ciclopropil-1-[1-(4-dimetilaminopiperidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(39) 1-{1-[1-(4-acetilaminopiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(40) 1-{1-[1-(3-acetilaminopirrolidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(41) clorhidrato de 1-{5-ciclopropil-1-[1-(3-dimetilaminopirrolidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(42) clorhidrato de 1-{5-ciclopropil-1-[1-(1-metilpiperidin-4-il-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(43) 1-{1-[1-(1-acetilpiperidin-4-il-carbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(44) 1-{5-ciclopropil-1-[1-(4-oxopiperidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(45) 1-{1-[1-(3-acetilaminoazetidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(46) 1-{5-ciclopropil-1-[1-(3-oxopirrolidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(47) 1-{5-ciclopropil-1-[1-(2,2,2-trifluoroetilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(48) 1-{5-ciclopropil-1-[1-(3,3,4,4-tetrafluoropirrolidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(49) 1-(5-ciclopropil-1-{1-[(S)-1-hidroximetil-2-metilpropil-carbamoil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(50) 1-(1-{1-[(S)-1-bencil-2-hidroxietilcarbamoil]piperidin-4-il}-5-

ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(51) 1-(5-ciclopropil-1-{1-[(S)-2-hidroxi-1-feniletilcarbamoil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(52) 1-(5-ciclopropil-1-{1-[(S)-1-hidroximetil-3-metilbutil-carbamoil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(53) 1-{5-ciclopropil-1-[1-(2-hidroxifenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(54) 1-{5-ciclopropil-1-[1-(1-hidroximetilciclopentilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(55) 1-[1-(1-bencensulfonilaminocarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(56) 1-[5-ciclopropil-1-(1-metansulfonilaminocarbonilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(57) 1-[5-ciclopropil-1-(1-metoxicarbonilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(58) 1-{5-ciclopropil-1-[1-(2-hidroxietoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(59) clorhidrato de 1-{5-ciclopropil-1-[1-(2-dimetil-aminoetoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometil-fenil)]pirrolidina,

(60) clorhidrato de 1-{5-ciclopropil-1-[1-(2-piperidin-1-il-etoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(61) clorhidrato de 1-{5-ciclopropil-1-[1-(piperidin-4-il-oxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(62) clorhidrato de 1-{5-ciclopropil-1-[1-(1-metilpiperidin-4-il-oxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(63) 1-{1-[1-(1-acetilpiperidin-4-il-oxicarbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(64) 1-[1-(1-ciclopropancarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(65) 1-{5-ciclopropil-1-[1-(2-hidroxiacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(66) 1-(5-ciclopropil-1-{1-[1-(4-fluorofenil)ciclopropancarbonil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(67) clorhidrato de 1-{5-ciclopropil-1-[1-(2-dimetilaminoacetil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(68) 1-{1-[1-(2-acetilaminoacetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(69) 1-{5-ciclopropil-1-[1-(1-metilciclopropancarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(70) 1-{1-[1-(2-acetilamino-2-metilpropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(71) 1-(1-{1-[(S)-2-acetilaminopropionil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(72) 1-(1-{1-[(S)-2-acetilamino-3-metilbutiril]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(73) 1-{5-ciclopropil-1-[1-(3,3,3-trifluoropropionil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(74) 1-(5-ciclopropil-1-{1-[(S)-5-oxopirrolidin-2-carbonil]piperidin-4-il}-

1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(75) 1-{1-[1-(3-acetilaminopropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(76) 1-{5-ciclopropil-1-[1-(3-hidroxi-2,2-dimetilpropionil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(77) clorhidrato de 1-{1-[1-(2-aminoacetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(78) 1-{5-ciclopropil-1-[1-(1-hidroximetilciclopropancarbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(79) clorhidrato de 1-{1-[1-(2-amino-2-metilpropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(80) 1-{5-ciclopropil-1-[1-(4-hidroxibutiril)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(81) clorhidrato de 1-(5-ciclopropil-1-{1-[(S)-pirrolidin-2-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(82) clorhidrato de 1-(5-ciclopropil-1-{1-[(S)-1-metilpirrolidin-2-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(83) clorhidrato de 1-{1-[1-(3-aminopropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(84) clorhidrato de 1-(1-{1-[(S)-2-amino-3-metilbutiril]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(85) clorhidrato de 1-{5-ciclopropil-1-[1-(2-metilaminoacetil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(86) clorhidrato de 1-{5-ciclopropil-1-[1-(piperidin-4-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(87) 1-{5-ciclopropil-1-[1-(2-isobutirilaminoacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(88) 1-{1-[1-(2-ciclopropancarbonilaminoacetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(89) 1-(1-{1-[(S)-1-acetilpirrolidin-2-carbonil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(90) 1-{5-ciclopropil-1-[1-(2-metansulfonilaminoacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(91) 1-{1-[1-(1-acetilpiperidin-4-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(92) clorhidrato de 1-{5-ciclopropil-1-[1-(1-metilpiperidin-4-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(93) 1-{1-[1-(3-carbamoilpropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(94) clorhidrato de 1-[1-(1-carbamoilmetilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(95) clorhidrato de 1-[5-ciclopropil-1-(1-metilcarbamoil-metilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(96) clorhidrato de 1-{1-[1-(1-carbamoil-1-metiletil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(97) clorhidrato de 1-{1-[1-(2-carbamoiletil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(98) clorhidrato de 1-[5-ciclopropil-1-(1-ciclopropilmetilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(99) clorhidrato de 1-[5-ciclopropil-1-(1-ciclopropilpiperidin-4-il)-1H-

pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(100) clorhidrato de 1-[5-ciclopropil-1-(1-dimetilcarbamoilmetil-piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(101) clorhidrato de 1-[1-(1-carboximetilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(102) clorhidrato de 1-[1-(1-carboxietilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(103) clorhidrato de 1-{1-[1-(1-carbamoiletil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(104) clorhidrato de 1-{1-[1-(2-carboxi-2-metilpropil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(105) clorhidrato de 1-{1-[1-(2-carbamoil-2-metilpropil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(106) clorhidrato de 1-{1-[1-(1-carbamoilciclopropilmetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(107) clorhidrato de 1-(5-ciclopropil-1-{1-[1-(2-hidroxietilcarbamoil)ciclopropilmetil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(108) 1-[5-ciclopropil-1-(1-trifluorometansulfonilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(109) 1-{5-ciclopropil-1-[1-(2,2,2-trifluoroetansulfonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(110) 1-{1-[1-(1-cianoiminoetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(111) 1-(1-{1-[cianoimino(metilamino)metil]piperidin-4-il}-5-ciclopropil-

1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(112) 1-{1-[1-(N-cianocarbamimidoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(113) ácido 4-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoico,

(114) ácido 3-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoico,

(115) ácido 5-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiofen-2-carboxílico,

(116) ácido 2-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiazol-4-carboxílico,

(117) clorhidrato de 1-{5-ciclopropil-1-[1-(5-metil-4H-[1,2,4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(118) clorhidrato de 1-{5-ciclopropil-1-[1-(5-ciclopropil-4H-[1,2,4]-triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(119) clorhidrato de 1-{5-ciclopropil-1-[1-(5-hidroximetil-4H-[1,2,4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(120) clorhidrato de 1-{5-ciclopropil-1-[1-(5-trifluorometil-4H-[1,2,4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(121) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(R)-3-(2-trifluorometilfenil)]pirrolidina,

(122) 1-{5-ciclopropil-1-[1-(1-metilciclopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(R)-3-(2-trifluorometilfenil)]pirrolidina,

(123) 1-{5-ciclopropil-1-[1-(1-isopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(R)-3-(2-trifluorometilfenil)]pirrolidina,

(124) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(125) 1-{5-ciclopropil-1-[1-(1-isopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(126) 1-{5-ciclopropil-1-[1-(1-metilciclopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(127) clorhidrato de (-)-3-(4-fluorofenil)-3-hidroximetil-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}-pirrolidina,

(128) clorhidrato de (+)-3-(4-fluorofenil)-3-hidroximetil-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}-pirrolidina,

(129) clorhidrato de 1-[5-ciclopropil-1-(1-pyrazin-2-il-piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(130) 1-[1-(trans-4-carbamoilciclohexil)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(131) 1-[5-ciclopropil-1-(trans-4-ureidociclohexil)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(132) 1-{5-ciclopropil-1-[trans-4-(1H-tetrazol-5-il)ciclohexil]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(133) 1-{5-(1-metilciclopropil)-1-[1-(4-trifluorometilfenilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(134) 1-{1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-5-(1-metoxiciclopropil)-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(135) 1-{1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-5-(1-metilciclopropil)-

1H-pirazol-4-carbonil}-3-fenil-3-trifluorometil-pirrolidina,

(136) 3-(2-clorofenil)-1-{5-ciclopropil-1-[1-(2,4-difluorofenil-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina,

(137) 3-(2-cloropiridin-3-il)-1-{5-ciclopropil-1-[1-(2-fluorofenil-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina,

(138) 1-{1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-5-(2,2,3,3-tetrametilciclopropil)-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(139) 1-{5-ciclohexil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(140) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometoxifenil)pirrolidina,

(141) 1-{5-ciclopropil-1-[1-(4-trifluorometilfenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(142) 1-(5-ciclopropil-1-{1-[((S)-1-carboxi-2-metilpropil)-metilcarbamoil]piperidin-4-il}-1H-pirazol-4-carbonil)-3-(2-trifluorometilfenil)-pirrolidina,

(143) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-metoxi-3-(2-trifluorometilfenil)pirrolidina,

(144) 1-{1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-5-(1-hidroximetilciclopropil)-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(145) 1-{5-ciclopropil-1-[1-(tiazol-2-ilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(146) 1-{1-[1-(isopropoxicarbamoil)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(147) 1-{5-ciclopropil-1-[1-(4-fluorobencilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(148) 1-{1-[1-(2,3-dihidroindol-1-carbonil)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(149) 1-{1-[1-(2,3-dihidro[1,4]oxazin-4-carbonil)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(150) 1-{5-ciclopropil-1-[1-(2,6-dichloropiridin-3-ilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(151) 1-{5-(1-metilciclopropil)-1-[1-(2,3,4,5-tetrahidrobenzo[b]-azepin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(152) 4-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoato de etilo,

(153) 1-[1-(1-benciloxicarbonil-piperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-3-(piridin-3-il)pirrolidina,

(154) 1-{1-[1-(3-carboxi-3-metil-butiril)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(155) 1-{5-ciclopropil-1-[1-(2-fenoxiacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(156) 1-{1-[1-(3-clorobenzoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(157) 1-{1-[1-(2-clorobenzoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(158) 1-[5-ciclopropil-1-(1-oxalilpiperidin-4-il)-1H-pirazol-4-carbonil]-3-(2-trifluorometilfenil)pirrolidina,

(159) 1-{1-[1-(4-clorobenzoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(160) 1-(5-ciclopropil-1-{1-[2-(4-fluorofenil)acetil]piperidin-4-il}-1H-

pirazol-4-carbonil)-3-(piridin-3-il)pirrolidina,

(161) 1-{5-ciclopropil-1-[1-(3-trifluorometilbenzoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(162) 1-{5-ciclopropil-1-[1-(3-metoxibenzoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(163) clorhidrato de 1-{1-[1-(4-fluorobencil)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(164) 1-[1-(1-bencensulfonil-piperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-3-(piridin-3-il)pirrolidina,

(165) 1-{1-[1-(4-carbamoilfenil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(166) 1-{5-ciclopropil-1-[1-(4-hidroximetilfenil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(167) 1-{1-[1-(5-carbamoil-piridin-2-il)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(168) 1-{1-[1-(4-aminofenil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(169) 1-(5-ciclopropil-1-{1-[4-(2-oxooxazolidin-3-il)fenil]piperidin-4-il}-1H-pirazol-4-carbonil)-3-(2-trifluorometilfenil)pirrolidina,

(170) 1-(5-ciclopropil-1-{1-[4-(3-metoxiureido)fenil]piperidin-4-il}-1H-pirazol-4-carbonil)-3-(2-trifluorometilfenil)pirrolidina,

(171) 1-{5-ciclopropil-1-[1-(4-metansulfonilaminofenil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(172) 1-[1-(1-etoxicarbamoilpiperidin-4-il)-5-(1-metilciclopropil)-1H-pirazol-4-carbonil]-3-(2-trifluorometilfenil)pirrolidina,

(173) 1-[1-(5-cloropiridin-2-il)azetidin-3-il]-5-ciclopropil-1H-pirazol-4-carbonil]-3-(2-trifluorometilfenil)pirrolidina,

(174) 1-{1-[1-(5-cloro-piridin-2-il)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-metoximetil-3-fenilpirrolidina,

(175) 1-{1-[1-(5-ciano-piridin-2-il)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(176) clorhidrato de 3-(2-acetoxietil)-3-(4-fluorofenil)-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}-pirrolidina,

(177) clorhidrato de {(3S*,4R*)-3-metil-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}-4-fenilpirrolidina,

(178) 6-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)nicotinato de metilo,

(179) 2-{1-[5-(1-metilciclopropil)-1-(1-pirimidin-2-il-piperidin-4-il)-1H-pirazol-4-carbonil]pirrolidin-3-il}benzoato de metilo,

(180) clorhidrato de 3-(2-hidroximetilfenil)-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}-pirrolidina,

(181) 1-[5-ciclopropil-1-(1-piridin-2-il-piperidin-4-il)-1H-pirazol-4-carbonil]-3-hidroxi-3-(piridin-3-il)pirrolidina,

(182) 1-{1-[1-(4-acetilaminofenil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina,

(183) 4-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)-3-fluorobenzoato de sodio,

(184) 3-(2-cianofenil)-1-{5-ciclopropil-1-[1-(2-fluorofenil-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina,

(185) clorhidrato de 3-hidroximetil-1-{1-[1-(4-metoxipirimidin-2-

il)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-fenilpirrolidina,

(186) clorhidrato de 3-(3,5-difluorofenil)-3-hidroximetil-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}-pirrolidina,

(187) 1-{1-[1-(3-cloro-piridin-2-il)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(188) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(tiazol-2-il)pirrolidina,

(189) ácido (S)-2-[(trans-4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)-pirrolidin-1-carbonil]-pirazol-1-il}-ciclohexancarbonil)-metil-amino]-3-metilbutírico,

(190) 1-{5-(1-metilciclopropil)-1-[trans-4-(2-fluorofenilcarbamoil)-ciclohexil]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina, y

(191) ácido cis-4-{5-(1-metilciclopropil)-4-[3-(2-trifluorometilfenil)-pirrolidin-1-carbonil]-pirazol-1-il)-ciclohexancarboxílico.

13. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de 1 a 12 indicado precedentemente o una sal del mismo.

14. Un inhibidor de 11βHSD1 que comprende un compuesto de acuerdo con cualquiera de 1 a 12 indicado precedentemente o una sal del mismo.

15. Un agente para el tratamiento o profilaxis de una patología que involucra glucocorticoide que comprende un compuesto de acuerdo con cualquiera de los 1 a 12 indicados precedentemente o una sal del mismo.

16. El agente del 15 indicado precedentemente, en donde la patología que involucra el glucocorticoide es

(1) una enfermedad metabólica que incluye diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión o hígado graso,

(2) un síndrome metabólico,

(3) un evento vascular fatal que incluye infarto cardíaco o apoplejía cerebral,

(4) hiperorexia,

(5) una enfermedad neurodisfuncional inclusive disgnosia, enfermedad neurodegenerativa, desórdenes emocionales, esquizofrenia o estímulo del apetito,

(6) una enfermedad asociada con la función de inmunidad disminuida,

(7) glaucoma, o

(8) osteoporosis.

17. Un método para inhibir 11βHSD1 que comprende administrar una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con cualquiera de 1 a 12 indicados precedentemente o una sal del mismo.

18. Un método para tratar o prevenir una patología que involucra glucocorticoide que comprende administrar una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con cualquiera de 1 a 12 indicados precedentemente o una sal del mismo.

19. El método del 18 indicado precedentemente, en donde la patología que involucra el glucocorticoide es

(1) una enfermedad metabólica que incluye diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión o hígado graso,

(2) un síndrome metabólico,

(3) un evento vascular fatal que incluye infarto cardíaco o apoplejía cerebral,

(4) hiperorexia,

(5) una enfermedad neurodisfuncional que incluye disgnosia, enfermedad neurodegenerativa, desórdenes emocionales, esquizofrenia o estímulo del apetito,

(6) una enfermedad asociada con la función de inmunidad disminuida,

(7) glaucoma, o

(8) osteoporosis.

20. El uso de un compuesto de acuerdo con cualquiera de 1 a 12 indicados precedentemente o una sal del mismo para la producción de un inhibidor de 11βHSD1.

21. El uso de un compuesto de acuerdo con cualquiera de 1 a 12 indicados precedentemente o una sal del mismo para la producción de un agente para el tratamiento o profilaxis de una patología que involucra glucocorticoide.

22. El uso del 21 indicado precedentemente, en donde la patología que involucra el glucocorticoide es

(1) una enfermedad metabólica que incluye diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión o hígado graso,

(2) un síndrome metabólico,

(3) un evento vascular fatal que incluye infarto cardíaco o apoplejía cerebral,

(4) hiperorexia,

(5) una enfermedad neurodisfuncional que incluye disgnosia, enfermedad neurodegenerativa, desórdenes emocionales, esquizofrenia o estímulo del apetito,

(6) una enfermedad asociada con la función de inmunidad disminuida,

(7) glaucoma, o

(8) osteoporosis.

23. Un paquete comercial que comprende un material escrito que declara que la composición farmacéutica de 13 indicado precedentemente puede o debe ser usado para el tratamiento o profilaxis de una enfermedad seleccionada de

(1) una enfermedad metabólica que incluye diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión o hígado graso,

(2) un síndrome metabólico,

(3) un evento vascular fatal que incluye infarto cardíaco o apoplejía cerebral,

(4) hiperorexia,

(5) una enfermedad neurodisfuncional que incluye disgnosia, enfermedad neurodegenerativa, desórdenes emocionales, esquizofrenia o estímulo del apetito,

(6) una enfermedad asociada con la función de inmunidad disminuida,

(7) glaucoma, o

(8) osteoporosis.

24. La composición farmacéutica del 13 indicado precedentemente a ser usada en la combinación con 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones

diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

25. El inhibidor de 11βHSD1 indicado precedentemente en 14, a ser utilizado en combinación con 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

26. El agente indicado precedentemente en 15 o 16, el cual será utilizado en combinación con 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

27. El método del 17 indicado precedentemente, que comprende administrar además 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

28. Un agente farmacéutico que comprende a 1 a 3 agentes seleccionados de los siguientes (1) a (5) y un compuesto de acuerdo con cualquiera de 1 a 12 indicados precedentemente o una sal del mismo en combinación:

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

29. Un método para tratar o prevenir una patología que involucra el glucocorticoide de 18 o 19 indicados precedentemente, el cual además comprende administrar de 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

30. El uso del 20 indicado precedentemente, el cual será combinado con el uso de 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones

diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

31. El uso del 21 ó 22 indicado precedentemente, el cual será combinado con el uso de 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

32. La composición farmacéutica del 13 indicado precedentemente la cual es utilizada para suprimir el incremento del nivel de glucocorticoide en la sangre por utilización en combinación con un agente farmacéutico que eleva el nivel de glucocorticoide de la sangre.

33. El inhibidor de 11βHSD1 del 14 indicado precedentemente que es utilizado para suprimir el incremento del nivel de glucocorticoide de la sangre por utilización de una combinación con un agente farmacéutico eleva el nivel de glucocorticoide de la sangre.

34. El método del 17 indicado precedentemente, el cual además comprende administrar un agente farmacéutico que eleva el nivel de glucocorticoide de la sangre.

35. El uso del 21 indicado precedentemente para suprimir el incremento del nivel de glucocorticoide de la sangre utilizando una combinación con un agente farmacéutico que eleva el nivel de glucocorticoide de la sangre.

36. Un método para suprimir el incremento del nivel de glucocorticoide

de la sangre que comprende administrar un agente farmacéutico que eleva el nivel de glucocorticoide de la sangre y el inhibidor de 11βHSD1 de 14 indicado precedentemente.

37. El 2-[(S)-2-nitro-1-(2-trifluorometilfenil)etil]malonato de dimetilo.

38. El (S)-2-oxo-4-(2-trifluorometilfenil)pirrolidin-3-carboxilato de metilo.

39. (S)-4-(2-trifluorometilfenil)pirrolidin-2-ona.

40. (S)-3-(2-trifluorometilfenil)pirrolidina o una sal de la misma.

41. Un método para producir 2-[(S)-2-nitro-1-(2-trifluorometilfenil)etil]malonato de dimetilo que comprende una etapa para hacer reaccionar 1-((E)-2-nitrovinil)-2-trifluorometilbenceno con malonato de dimetilo en presencia de 1-(3,5-bis-trifluorometilfenil)-3-((1S,2S)-2-dimetilaminociclohexil)-tiourea.

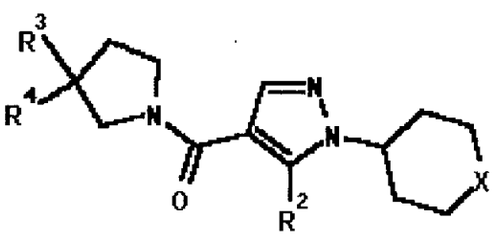
42. Un método para producir (S)-2-oxo-4-(2-trifluorometilfenil)pirrolidin-3-carboxilato de metilo que comprende una etapa para la reducción y cierre del anillo de 2-[(S)-2-nitro-1-(2-trifluorometilfenil)etil]malonato de dimetilo.

43. Un método para producir (S)-4-(2-trifluorometilfenil)pirrolidin-2-ona que comprende una etapa para la hidrólisis y descarbonación de (S)-2-oxo-4-(2-trifluorometilfenil)pirrolidin-3-carboxilato de metilo.

44. Un método para producir una sal de (S)-3-(2-trifluorometilfenil)pirrolidina que comprende una etapa para la reducción de (S)-4-(2-trifluorometilfenil)pirrolidin-2-ona y una etapa para tratar el compuesto resultante con un ácido para formar una sal.

La presente invención también abarca lo siguiente.

45. Un compuesto representado por la fórmula siguiente [2]:



[1]

en donde

-X- es

(1) -N(R^1)- en donde R^1 es

1) un átomo de hidrógeno,

2) -CONR^{5}R^6 en donde R^5 y R^6 son iguales o diferentes y cada uno es

(a) un átomo de hidrógeno,

(b) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo carboxilo,

d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y

e) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})),

(d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes

seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv):

(i) un átomo de halógeno,

(ii) un grupo hidroxilo,

(iii) un grupo oxo, y

(iv) un grupo alcoxilo de C_{1-6}),

e) un grupo alcoxilo de C_{1-6}, y

f) un grupo carboxilo),

(e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, o

(f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno

(dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo), o

(g) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o un grupo heterocíclico que es un anillo fusionado de dicho heterociclo y un anillo de carbono (ambos grupos heterocíclicos mencionados son sustituidos opcionalmente por uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}),

d) un grupo carboxilo,

e) un grupo -CO-alquilo de C_{1-6},

f) $-CO-NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

g) un grupo oxo,

h) $-NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es

un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

i) un grupo alcoxilo de C_{1-6}),

3) $-COOR^{10}$ en donde R^{10} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo hidroxilo,

b) $-NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

c) un grupo alcoxilo de C1-6), o

(b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

4) $-COR^{11}$ en donde R^{11} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al g):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

d) $-CO-NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

e) un grupo alcoxilo de C_{1-6},

f) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo alcoxilo de C_{1-6}, y (iv) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y

g) un grupo carboxilo),

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b):

a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y

b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), o

(c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

5) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (d):

(a) un grupo carboxilo,

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno),

(c) -CO-$NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico

monocíclico saturado que contiene nitrógeno, y

(d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes))),

6) un grupo cicloalquilo,

7) $-S(=O)_2-R^{12}$ en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

8) $-C(=NCN)-R^{13}$ en donde R^{13} es un grupo alquilo de C_{1-6},

9) $-C(=NCN)NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

10) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (f):

(a) un grupo carboxilo,

(b) un átomo de halógeno,

(c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, y c) un grupo alcoxilo de C_{1-6}),

(d) $-NR^{38}R^{39}$ en donde R^{38} y R^{39} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, $-CO-NR^{40}R^{41}$ en donde R^{40} y R^{41} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo alcoxilo de C_{1-6}, o R^{40} y R^{41} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o $-S(=O)_2-R^{42}$ en donde R^{42} es un grupo alquilo de C_{1-6}), o R^{38} y R^{39} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más grupos oxo),

(e) $-CO-NR^{43}R^{44}$ en donde R^{43} y R^{44} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{43} y R^{44} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

(f) un grupo -COO-alquilo de C_{1-6}), o

11) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (g):

(a) un grupo carboxilo,

(b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un átomo de halógeno,

b) un grupo hidroxilo, y

c) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo,

(d) un átomo de halógeno,

(e) -CO-$NR^{45}R^{46}$ en donde R^{45} y R^{46} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{45} y R^{46} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

(f) un grupo -COO-alquilo de C_{1-6}, y

(g) un grupo ciano), o

(2) -$C(R^7R^8)$- en donde R^7 y R^8 son iguales o diferentes y cada uno es

1) un átomo de hidrógeno,

2) -$NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o -CO-$NR^{36}R^{37}$ en donde R^{36} y R^{37} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{36} y R^{37} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o R^{16} y R^{17} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

3) -$CONR^{18}R^{19}$ en donde R^{18} y R^{19} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más grupos carboxilo), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un átomo de halógeno, y (b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o R^{18} y R^{19} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico

monocíclico saturado que contiene nitrógeno,

4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros, o

5) un grupo carboxilo;

R^2 es

(1) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un grupo hidroxilo, y (b) un grupo alcoxilo de C_{1-6})); y R^3 y R^4 son iguales o diferentes y cada uno es

(1) un átomo de hidrógeno,

(2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un átomo de halógeno, 2) un grupo hidroxilo, y 3) un grupo alcoxilo de C_{1-6}),

(3) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente 1) a 6):

1) un átomo de halógeno,

2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un átomo de halógeno, (b) un grupo hidroxilo, y (c) un grupo alcoxilo de C_{1-6}),

3) un grupo alcoxilo de C_{1-6} (dicho grupo alcoxilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes),

4) un grupo carboxilo,

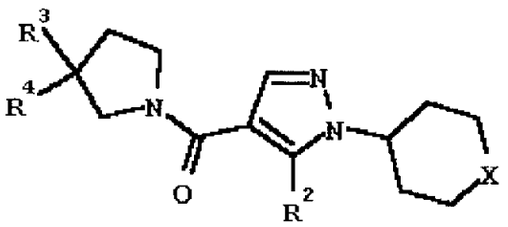
5) un grupo -COO-alquilo de C_{1-6}, y

6) un grupo ciano), o

(4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un átomo de halógeno, y 2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

o una sal del mismo.

46. El compuesto del indicado precedentemente 45 que se representa por la fórmula siguiente [2]:



[2]

en donde

-X- es

(1) $-N(R^1)-$ en donde R^1 es

1) un átomo de hidrógeno,

2) $-CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es

(a) un átomo de hidrógeno,

(b) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo carboxilo,

d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y

e) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})),

(d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv):

(i) un átomo de halógeno,

(ii) un grupo hidroxilo,

(iii) un grupo oxo, y

(iv) un grupo alcoxilo de C_{1-6}), y

e) un grupo alcoxilo de C_{1-6}),

(e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, o

(f) un grupo heterociclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo), o

(g) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de

C_{1-6}),

d) un grupo carboxilo,

e) un grupo -CO-alquilo de C_{1-6},

f) -CO-$NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

g) un grupo oxo,

h) -$NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

i) un grupo alcoxilo de C_{1-6}),

3) -$COOR^{10}$ en donde R^{10} es,

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo hidroxilo,

b) -$NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

c) un grupo alcoxilo de C_{1-6}), o

(b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más

sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

4) $-COR^{11}$ en donde R^{11} es,

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al e):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

d) $-CO-NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

e) un grupo alcoxilo de C_{1-6}),

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b):

a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2):

(1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y

b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), o

(c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

5) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (c):

(a) un grupo carboxilo,

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno), y

(c) -CO-$NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno),

6) un grupo cicloalquilo,

7) -$S(=O)_2$-R^{12} en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes),

8) -C(=NCN)-R^{13} en donde R^{13} es un grupo alquilo de C_{1-6},

9) -C(=NCN)$NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

10) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) a (3): (1) un átomo de halógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), y (3) un grupo carboxilo), o

11) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (c):

(a) un grupo carboxilo,

(b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un átomo de halógeno,

b) un grupo hidroxilo, y

c) un grupo alcoxilo de C_{1-6}), y

(c) un grupo cicloalquilo), o

(2) $-C(R^7R^8)-$ en donde R^7 y R^8 son iguales o diferentes y cada uno es

1) un átomo de hidrógeno,

2) $-NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o $-CO-NR^{36}R^{37}$ en donde R^{36} y R^{37} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{36} y R^{37} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o R^{16} y R^{17} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

3) $-CONR^{18}R^{19}$ en donde R^{18} y R^{19} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{18} y R^{19} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o

4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros;

R^2 es

(1) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes); y

R^3 y R^4 son iguales o diferentes y cada uno es

(1) un átomo de hidrógeno,

(2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es

opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}),

(3) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente 1) y 2):

1) un átomo de halógeno, y

2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o

(4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros,

o una sal del mismo.

47. El compuesto del 45 o 46 indicado precedentemente, en donde -X- es $-C(R^7R^8)-$ en donde R^7 y R^8 es igual al definido en el 46 indicado precedentemente, o una sal del mismo.

48. El compuesto de acuerdo con cualquiera de 45 a 47 indicados precedentemente, en donde R^8 es

1) $-NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{16} y R^{17} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

2) $-CONR^{18}R^{19}$ en donde R^{18} y R^{19} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{18} y R^{19} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o

3) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de

6 miembros),

o una sal del mismo.

49. El compuesto del 45 o 46 indicados precedentemente, en donde -X- es -N(R^1)- en donde R^1 es igual al definido en el 46) indicado precedentemente, o una sal del mismo.

50. El compuesto de acuerdo con cualquiera de 45, 46 y 49 indicado precedentemente, en donde R^1 es

1) un átomo de hidrógeno,

2) -$CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es

(a) un átomo de hidrógeno,

(b) un grupo arilo (dicho grupo arilo es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo carboxilo,

d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y

e) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})),

(d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv):

(i) un átomo de halógeno,

(ii) un grupo hidroxilo,

(iii) un grupo oxo, y

(iv) un grupo alcoxilo de C_{1-6}), y

e) un grupo alcoxilo de C_{1-6}),

(e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, o

(f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno

(dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo), o

(g) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}),

d) un grupo carboxilo,

e) un grupo -CO-alquilo de C_{1-6},

f) -CO-$NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

g) un grupo oxo,

h) -$NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un

grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

i) un grupo alcoxilo de C_{1-6}) (con la condición que R^5 y R^6 no sean simultáneamente átomos de hidrógeno),

3) -$COOR^{10}$ en donde R^{10} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo hidroxilo,

b) -$NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

c) un grupo alcoxilo de C_{1-6}), o

(b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

4) -COR^{11} en donde R^{11} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al e):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

d) $-CO-NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

e) un grupo alcoxilo de C_{1-6}),

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b):

a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y

b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), o

(c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

5) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (c):

(a) un grupo carboxilo,

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno), y

(c) -CO-$NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno),

6) un grupo cicloalquilo,

7) -$S(=O)_2$-R^{12} en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes),

8) -C(=NCN)-R^{13} en donde R^{13} es un grupo alquilo de C_{1-6},

9) -C(=NCN)$NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y

cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

10) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) a (3): (1) un átomo de halógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), y (3) un grupo carboxilo), o

11) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (c):

(a) un grupo carboxilo,

(b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un átomo de halógeno,

b) un grupo hidroxilo, y

c) un grupo alcoxilo de C_{1-6}), y

(c) un grupo cicloalquilo),

o una sal del mismo.

51. El compuesto de acuerdo con cualquiera de indicado precedentemente 45, 46 y 49, en donde R^1 son

1) $-CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es

(a) un átomo de hidrógeno,

(b) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con

uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo carboxilo,

d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y

e) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})),

(d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20}

y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv):

(i) un átomo de halógeno,

(ii) un grupo hidroxilo,

(iii) un grupo oxo, y

(iv) un grupo alcoxilo de C_{1-6}), y

e) un grupo alcoxilo de C_{1-6}),

(e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, o

(f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo), o

(g) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}),

d) un grupo carboxilo,

e) un grupo -CO-alquilo de C_{1-6},

f) $-CO-NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

g) un grupo oxo,

h) $-NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

i) un grupo alcoxilo de C_{1-6}) (con la condición que R^5 y R^6 no son simultáneamente átomos de hidrógeno y grupo alquilo de C_{1-6} sin sustituir),

2) $-COOR^{10}$ en donde R^{10} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo hidroxilo,

b) $-NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman,

junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

c) un grupo alcoxilo de C_{1-6}), o

(b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

3) $-COR^{11}$ en donde R^{11} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al e):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

d) $-CO-NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

e) un grupo alcoxilo de C_{1-6}),

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b):

a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y

b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), o

(c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

4) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (c):

(a) un grupo carboxilo,

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes

iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno), y

(c) $-CO-NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno),

5) un grupo cicloalquilo,

6) $-S(=O)_2-R^{12}$ en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más átomos halógenos iguales o diferentes),

7) $-C(=NCN)-R^{13}$ en donde R^{13} es un grupo alquilo de C_{1-6},

8) $-C(=NCN)NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o

9) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) y (b):

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un átomo de halógeno,

b) un grupo hidroxilo, y

c) un grupo alcoxilo de C_{1-6}), y

(b) un grupo cicloalquilo),

o una sal del mismo.

52. El compuesto de acuerdo con cualquiera de 45, 46 y 49 indicados precedentemente, en donde R^1 es

1) $-CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es

(a) un átomo de hidrógeno,

(b) un grupo arilo (dicho grupo arilo es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo carboxilo,

d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y

e) un grupo alcoxilo de C_{1-6}),

(c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})),

(d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

a) un grupo hidroxilo,

b) un átomo de halógeno,

c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)),

d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv):

(i) un átomo de halógeno,

(ii) un grupo hidroxilo,

(iii) un grupo oxo, y

(iv) un grupo alcoxilo de C_{1-6}), y

e) un grupo alcoxilo de C_{1-6}),

(e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, o

(f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo), o

(g) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}),

d) un grupo carboxilo,

e) un grupo -CO-alquilo de C_{1-6},

f) -CO-$NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno,

g) un grupo oxo,

h) -$NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

i) un grupo alcoxilo de C_{1-6}) (con la condición que R^5 y R^6 no sean simultáneamente átomos de hidrógeno y grupo alquilo de C_{1-6} sin sustituir),

2) -$COOR^{10}$ en donde R^{10} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo hidroxilo,

b) $-NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

c) un grupo alcoxilo de C_{1-6}), o

(b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

3) - COR^{11} en donde R^{11} es

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al e):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico

monocíclico saturado que contiene nitrógeno,

d) -CO-$NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y

e) un grupo alcoxilo de C_{1-6}),

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b):

a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y

b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), o

(c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo),

4) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con

uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (c):

(a) un grupo carboxilo,

(b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno), y

(c) -CO-$NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno),

5) un grupo cicloalquilo,

6) -$S(=O)_2$-R^{12} en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más átomos halógenos iguales o diferentes),

7) -C(=NCN)-R^{13} en donde R^{13} es un grupo alquilo de C_{1-6},

8) -C(=NCN)$NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o

9) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) y (b):

(a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un átomo de halógeno,

b) un grupo hidroxilo, y

c) un grupo alcoxilo de C_{1-6}), y

(b) un grupo cicloalquilo),

o una sal del mismo.

53. El compuesto de acuerdo con cualquiera de 45 a 52 indicados precedentemente, en donde R^2 es un grupo ciclopropilo o es un grupo 1-metilciclopropilo, o una sal del mismo.

54. El compuesto de acuerdo con cualquiera de 45 a 53 indicados precedentemente, en donde R^3 y R^4 son iguales o diferentes y cada uno es

(1) un átomo de hidrógeno,

(2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}),

(3) un grupo fenilo (dicho grupo fenilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente 1) y 2):

1) un átomo de halógeno, y

2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o

(4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros,

o una sal del mismo.

55. El compuesto del 45 indicado precedentemente o una sal del mismo que es seleccionado de los siguientes:

(1) 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-3-(piridin-3-il)pirrolidina,

(2) clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(3) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina,

(4) 1-[1-(1-carbamoilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(5) 1-{1-[1-(2-carboxifenilcarbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(6) 1-{5-ciclopropil-1-[1-(2-hidroximetilfenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(7) 1-{5-ciclopropil-1-[1-(1-hidroximetilciclopropilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(8) 1-{5-ciclopropil-1-[1-(2-hidroxietilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(9) 1-{5-ciclopropil-1-[1-(2-hidroxi-1,1-dimetiletilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(10) 1-{1-[1-(2-acetilaminoetilcarbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(11) clorhidrato de 1-{1-[1-(2-aminoetilcarbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(12) 1-{5-ciclopropil-1-[1-(1,1-dioxotiomorfolina-4-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(13) clorhidrato de 1-{5-ciclopropil-1-[1-(2-dimetil-aminoetilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(14) 1-{5-ciclopropil-1-[1-(4-hidroxipiperidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(15) 1-{1-[1-(azetidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(16) 1-{5-ciclopropil-1-[1-(3-hidroxipirrolidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(17) clorhidrato de 1-{5-ciclopropil-1-[1-(2-piperidin-1-il-etilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(18) 1-{5-ciclopropil-1-[1-(4,4-difluoropiperidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(19) 1-{5-ciclopropil-1-[1-(3,3-difluoropirrolidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(20) 1-{5-ciclopropil-1-[1-(3-hidroxiazetidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(21) 1-(5-ciclopropil-1-{1-[(R)-3-hidroxipirrolidin-1-carbonil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(22) 1-(5-ciclopropil-1-{1-[(S)-3-hidroxipirrolidin-1-carbonil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(23) 1-(5-ciclopropil-1-{1-[(S)-2-hidroxi-1-metietilarbamoil]-piperidin-4-

il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(24) 1-{5-ciclopropil-1-[1-(4-hidroximetilpiperidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(25) 1-{1-[1-(4-carboxipiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(26) 1-{5-ciclopropil-1-[1-(3-oxopiperazin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(27) 1-(5-ciclopropil-1-{1-[(S)-2-hidroximetilpirrolidin-1-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(28) 1-{5-ciclopropil-1-[1-(3-hidroximetilazetidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(29) clorhidrato de 1-{5-ciclopropil-1-[1-(4-metilpiperazin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(30) clorhidrato de 1-{5-ciclopropil-1-[1-(4-isopropilpiperazin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(31) 1-{1-[1-(4-acetilpiperazin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(32) 1-(5-ciclopropil-1-{1-[(R)-3-hidroxipiperidin-1-carbonil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(33) 1-{1-[1-(4-carbamoilpiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(34) 1-{1-[1-(3-carbamoilazetidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(35) clorhidrato de 1-{1-[1-(4-aminopiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

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(36) clorhidrato de 1-{1-[1-(3-aminopirrolidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(37) clorhidrato de 1-{5-ciclopropil-1-[1-(piperidin-4-il-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(38) clorhidrato de 1-{5-ciclopropil-1-[1-(4-dimetilaminopiperidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(39) 1-{1-[1-(4-acetilaminopiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(40) 1-{1-[1-(3-acetilaminopirrolidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(41) clorhidrato de 1-{5-ciclopropil-1-[1-(3-dimetilaminopirrolidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(42) clorhidrato de 1-{5-ciclopropil-1-[1-(1-metilpiperidin-4-il-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(43) 1-{1-[1-(1-acetilpiperidin-4-il-carbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(44) 1-{5-ciclopropil-1-[1-(4-oxopiperidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(45) 1-{1-[1-(3-acetilaminoazetidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(46) 1-{5-ciclopropil-1-[1-(3-oxopirrolidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(47) 1-{5-ciclopropil-1-[1-(2,2,2-trifluoroetilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(48) 1-{5-ciclopropil-1-[1-(3,3,4,4-tetrafluoropirrolidin-1-carbonil)-

piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(49) 1-(5-ciclopropil-1-{1-[(S)-1-hidroximetil-2-metilpropil-carbamoil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(50) 1-(1-{1-[(S)-1-bencil-2-hidroxietilcarbamoil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(51) 1-(5-ciclopropil-1-{1-[(S)-2-hidroxi-1-feniletilcarbamoil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(52) 1-(5-ciclopropil-1-{1-[(S)-1-hidroximetil-3-metil-butilcarbamoil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(53) 1-{5-ciclopropil-1-[1-(2-hidroxifenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(54) 1-{5-ciclopropil-1-[1-(1-hidroximetilciclopentilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(55) 1-[1-(1-bencensulfonilaminocarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(56) 1-[5-ciclopropil-1-(1-metansulfonilaminocarbonilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(57) 1-[5-ciclopropil-1-(1-metoxicarbonilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(58) 1-{5-ciclopropil-1-[1-(2-hidroxietoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(59) clorhidrato de 1-{5-ciclopropil-1-[1-(2-dimetilaminoetoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(60) clorhidrato de 1-{5-ciclopropil-1-[1-(2-piperidin-1-il-etoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(61) clorhidrato de 1-{5-ciclopropil-1-[1-(piperidin-4-il-oxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(62) clorhidrato de 1-{5-ciclopropil-1-[1-(1-metilpiperidin-4-il-oxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(63) 1-{1-[1-(1-acetilpiperidin-4-il-oxicarbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(64) 1-[1-(1-ciclopropancarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(65) 1-{5-ciclopropil-1-[1-(2-hidroxiacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(66) 1-(5-ciclopropil-1-{1-[1-(4-fluorofenil)ciclopropancarbonil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(67) clorhidrato de 1-{5-ciclopropil-1-[1-(2-dimetilaminoacetil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(68) 1-{1-[1-(2-acetilaminoacetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(69) 1-{5-ciclopropil-1-[1-(1-metilciclopropancarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(70) 1-{1-[1-(2-acetilamino-2-metilpropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(71) 1-(1-{1-[(S)-2-acetilaminopropionil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

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(72) 1-(1-{1-[(S)-2-acetilamino-3-metilbutiril]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(73) 1-{5-ciclopropil-1-[1-(3,3,3-trifluoropropionil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(74) 1-(5-ciclopropil-1-{1-[(S)-5-oxopirrolidin-2-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(75) 1-{1-[1-(3-acetilaminopropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(76) 1-{5-ciclopropil-1-[1-(3-hidroxi-2,2-dimetilpropionil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(77) clorhidrato de 1-{1-[1-(2-aminoacetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(78) 1-{5-ciclopropil-1-[1-(1-hidroximetilciclopropancarbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(79) clorhidrato de 1-{1-[1-(2-amino-2-metilpropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(80) 1-{5-ciclopropil-1-[1-(4-hidroxibutiril)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(81) clorhidrato de 1-(5-ciclopropil-1-{1-[(S)-pirrolidin-2-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(82) clorhidrato de 1-(5-ciclopropil-1-{1-[(S)-1-metilpirrolidin-2-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(83) clorhidrato de 1-{1-[1-(3-aminopropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(84) 1-(1-{1-[(S)-2-amino-3-metilbutiril]piperidin-4-il}-5-ciclopropil-1H-

pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)] el clorhidrato de pirrolidina,

(85) clorhidrato de 1-{5-ciclopropil-1-[1-(2-metilaminoacetil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(86) clorhidrato de 1-{5-ciclopropil-1-[1-(piperidin-4-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(87) 1-{5-ciclopropil-1-[1-(2-isobutirilaminoacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(88) 1-{1-[1-(2-ciclopropancarbonilaminoacetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(89) 1-(1-{1-[(S)-1-acetilpirrolidin-2-carbonil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(90) 1-{5-ciclopropil-1-[1-(2-metansulfonilaminoacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(91) 1-{1-[1-(1-acetilpiperidin-4-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(92) clorhidrato de 1-{5-ciclopropil-1-[1-(1-metilpiperidin-4-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(93) 1-{1-[1-(3-carbamoilpropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(94) clorhidrato de 1-[1-(1-carbamoilmetilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(95) clorhidrato de 1-[5-ciclopropil-1-(1-metil-carbamoilmetilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(96) clorhidrato de 1-{1-[1-(1-carbamoil-1-metiletil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(97) clorhidrato de 1-{1-[1-(2-carbamoiletil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(98) clorhidrato de 1-[5-ciclopropil-1-(1-ciclopropilmetilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(99) clorhidrato de 1-[5-ciclopropil-1-(1-ciclopropilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(100) clorhidrato de 1-[5-ciclopropil-1-(1-dimetil-carbamoilmetilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina,

(101) clorhidrato de 1-[1-(1-carboximetilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(102) clorhidrato de 1-[1-(1-carboxietilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(103) clorhidrato de 1-{1-[1-(1-carbamoiletil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(104) clorhidrato de 1-{1-[1-(2-carboxi-2-metilpropil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(105) clorhidrato de 1-{1-[1-(2-carbamoil-2-metilpropil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(106) clorhidrato de 1-{1-[1-(1-carbamoilciclopropilmetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(107) clorhidrato de 1-(5-ciclopropil-1-{1-[1-(2-hidroxietil-carbamoil)ciclopropilmetil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(108) 1-[5-ciclopropil-1-(1-trifluorometansulfonilpiperidin-4-il)-1H-

pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(109) 1-{5-ciclopropil-1-[1-(2,2,2-trifluoroetansulfonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(110) 1-{1-[1-(1-cianoiminoetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(111) 1-(1-{1-[cianoimino(metilamino)metil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(112) 1-{1-[1-(N-cianocarbamimidoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(113) ácido 4-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoico,

(114) ácido 3-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoico,

(115) ácido 5-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiofen-2-carboxílico,

(116) ácido 2-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiazol-4-carboxílico,

(117) clorhidrato de 1-{5-ciclopropil-1-[1-(5-metil-4H-[1,2,4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(118) clorhidrato de 1-{5-ciclopropil-1-[1-(5-ciclopropil-4H-[1,2,4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(119) clorhidrato de 1-{5-ciclopropil-1-[1-(5-hidroximetil-4H-[1,2,4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(120) clorhidrato de 1-{5-ciclopropil-1-[1-(5-trifluorometil-4H-

[1,2,4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(121) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(R)-3-(2-trifluorometilfenil)]pirrolidina,

(122) 1-{5-ciclopropil-1-[1-(1-metilciclopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(R)-3-(2-trifluorometilfenil)]pirrolidina,

(123) 1-{5-ciclopropil-1-[1-(1-isopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(R)-3-(2-trifluorometilfenil)]pirrolidina,

(124) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(125) 1-{5-ciclopropil-1-[1-(1-isopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(126) 1-{5-ciclopropil-1-[1-(1-metilciclopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(127) clorhidrato de (-)-3-(4-fluorofenil)-3-hidroximetil-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}-pirrolidina,

(128) clorhidrato de (+)-3-(4-fluorofenil)-3-hidroximetil-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}-pirrolidina,

(129) clorhidrato de 1-[5-ciclopropil-1-(1-pirazin-2-il-piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(130) 1-[1-(trans-4-carbamoilciclohexil)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina,

(131) 1-[5-ciclopropil-1-(trans-4-ureidociclohexil)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina, y

(132) 1-{5-ciclopropil-1-[trans-4-(1H-tetrazol-5-il)ciclohexil]-1H-pirazol-

4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina.

56. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de 45 a 55 indicados precedentemente o una sal del mismo.

57. Un inhibidor de 11βHSD1 que comprende un compuesto de acuerdo con cualquiera de 45 a 55 indicados precedentemente o una sal del mismo.

58. Un agente para el tratamiento o profilaxis de una patología que involucra glucocorticoide que comprende un compuesto de acuerdo con cualquiera de 45 a 55 indicados precedentemente o una sal del mismo.

59. El agente del indicado precedentemente 58, en donde la patología que involucra glucocorticoide es

(1) una enfermedad metabólica que incluye diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión o hígado graso,

(2) un síndrome metabólico,

(3) un evento vascular fatal que incluye infarto cardíaco o apoplejía cerebral basada en tales enfermedades,

(4) hiperorexia,

(5) una enfermedad neurodisfuncional que incluye disgnosia, enfermedades neurodegenerativas acompañadas por la desaparición de células nerviosas, desórdenes emocionales que incluyen ansiedad, depresión o manía, esquizofrenia o estímulo del apetito,

(6) una enfermedad que requiere tratamiento o profilaxis de inmunidad disminuída o aumento de inmunidad, que incluye inmunodeficiencia,

(7) glaucoma, o

(8) osteoporosis.

60. Un método para inhibir 11βHSD1 que comprenden administrar una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con cualquiera de 45 a 55 indicados precedentemente o una sal del mismo.

61. Un método de tratar o prevenir una patología que involucra glucocorticoide que comprende administrar una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con cualquiera de 45 a 55 indicados precedentemente o una sal del mismo.

62. El método del 61 indicado precedentemente, en donde la patología que involucra glucocorticoide es

(1) una enfermedad metabólica que incluye diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión o hígado graso,

(2) un síndrome metabólico,

(3) un evento vascular fatal que incluye infarto cardíaco o apoplejía cerebral basada en tales enfermedades,

(4) hiperorexia,

(5) una enfermedad neurodisfuncional que incluye disgnosia, enfermedades neurodegenerativas acompañadas por desaparición de células nerviosas, desórdenes emocionales que incluyen ansiedad, depresión o manía, esquizofrenia o estímulo del apetito,

(6) una enfermedad que requiere tratamiento o profilaxis de inmunidad disminuída o aumento de inmunidad, incluyendo la inmunodeficiencia,

(7) glaucoma, o

(8) osteoporosis.

63. El uso de un compuesto de acuerdo con cualquiera de 45 a 55

indicados precedentemente o una sal del mismo para la producción de un inhibidor de 11βHSD1.

64. El uso de un compuesto de acuerdo con cualquiera de 45 a 55 indicados precedentemente o una sal del mismo para la producción de un agente para el tratamiento o profilaxis de una patología que involucra el glucocorticoide.

65. El uso del 64 indicado precedentemente, en donde la patología que involucra glucocorticoide es

(1) una enfermedad metabólica que incluye diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión o hígado graso,

(2) un síndrome metabólico,

(3) un evento vascular fatal que incluye infarto cardíaco o apoplejía cerebral basada en tales enfermedades,

(4) hiperorexia,

(5) una enfermedad neurodisfuncional que incluye disgnosia, enfermedades neurodegenerativas acompañadas por la desaparición de células nerviosas, desórdenes emocionales que incluyen ansiedad, depresión o manía, esquizofrenia o estímulo del apetito,

(6) una enfermedad que requiere tratamiento o profilaxis de inmunidad disminuída o aumento de inmunidad, incluyendo la inmunodeficiencia,

(7) el glaucoma, o

(8) la osteoporosis.

66. Un paquete comercial que comprende un material escrito que declara que la composición farmacéutica de 56 indicado precedentemente puede o debe ser usada para tratamiento o profilaxis de una enfermedad seleccionada de

(1) una enfermedad metabólica que incluye diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión o hígado graso,

(2) un síndrome metabólico,

(3) un evento vascular fatal que incluye infarto cardíaco o apoplejía cerebral basada en tales enfermedades,

(4) hiperorexia,

(5) una enfermedad neurodisfuncional que incluye disgnosia, enfermedades neurodegenerativas acompañadas por desaparición de células nerviosas, desórdenes emocionales que incluyen ansiedad, depresión o manía, esquizofrenia o estímulo del apetito,

(6) una enfermedad que requiere tratamiento o profilaxis de inmunidad disminuída o aumento de inmunidad, incluyendo inmunodeficiencia,

(7) glaucoma, y

(8) osteoporosis.

67. La composición farmacéutica del 56 indicado precedentemente a ser utilizada en combinación con 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

68. El inhibidor de 11βHSD1 del 57 indicado precedentemente, a ser

usado en combinación con 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

69. El agente del 58 o 59 indicados precedentemente, el cual va a ser utilizado en combinación con 1 a 3 agentes seleccionados de los siguiente (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

70. El método del 60 indicado precedentemente, que comprende además administrar de 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

71. Un agente farmacéutico que comprende a 1 a 3 agentes seleccionados de los siguientes (1) a (5) y un compuesto de acuerdo con cualquiera

de 45 a 55 indicados precedentemente o una sal del mismo en una combinación:

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

72. Un método de tratar o prevenir una patología que involucra glucocorticoide de acuerdo con 61 o 62 indicados precedentemente, el cual además comprende administrar de 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

73. El uso del 63 indicado precedentemente, el cual se combinará con el uso de 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

74. El uso del 64 o 65 indicado precedentemente, el cual se combinará

con el uso de 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

75. La composición farmacéutica del 56 indicado precedentemente, el cual será utilizado para suprimir el incremento de nivel de glucocorticoide de la sangre utilizado en combinación con un agente farmacéutico que eleva el nivel de glucocorticoide de la sangre.

76. El inhibidor de 11βHSD1 del 57 indicado precedentemente, el cual es utilizado para suprimir el incremento de nivel de glucocorticoide de la sangre utilizado en combinación con un agente farmacéutico que eleva el nivel de glucocorticoide de la sangre.

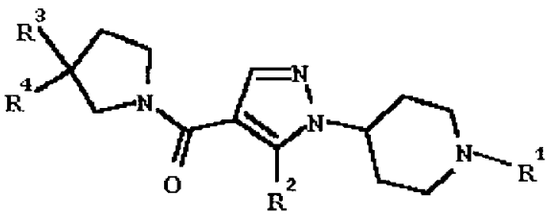
77. El método del 60 indicado precedentemente, el cual además comprende administrar un agente farmacéutico que eleva el nivel de glucocorticoide de la sangre.

78. El uso del 64 indicado precedentemente, para suprimir el incremento de nivel de glucocorticoide de la sangre utilizado en combinación con un agente farmacéutico que eleva el nivel de glucocorticoide de la sangre.

79. Un método para suprimir el incremento del nivel de glucocorticoide de la sangre que comprende administrar un agente farmacéutico que eleva el nivel de glucocorticoide de la sangre y el inhibidor de 11βHSD1 del 57 indicado precedentemente.

La presente invención comprende además lo siguiente.

80. Un compuesto representado por la fórmula siguiente [3]:



[3]

en donde

R^1 es

(1) $-CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es

1) un átomo de hidrógeno,

2) un grupo alquilo de C_{1-6},

3) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes), o

4) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes),

(2) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más grupos carboxilo), o

(3) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es opcionalmente sustituido con uno o más grupos carboxilo);

R^2 es

(1) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes); y

R^3 y R^4 son iguales o diferentes y cada uno es

(1) un átomo de hidrógeno,

(2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más grupos hidroxilo),

(3) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de un átomo de halógeno y un grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más átomos halógenos), o

(4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros,

o una sal farmacéuticamente aceptable del mismo.

81. El compuesto del 80 indicado precedentemente, en donde R^1 es

(1) $-CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es

1) un átomo de hidrógeno,

2) un grupo alquilo de C_{1-6},

3) un grupo ciclopropilo (dicho grupo ciclopropilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes), o

4) un grupo fenilo (dicho grupo fenilo es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes),

(2) un grupo fenilo (dicho grupo fenilo es opcionalmente sustituido con uno o más grupos carboxilo), o

(3) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterociclico es opcionalmente sustituido con uno o más grupos carboxilo), o una sal farmacéuticamente aceptable del mismo.

82. El compuesto del 80 indicado precedentemente, en donde R^2 es un grupo ciclopropilo o un grupo metilciclopropilo, o una sal farmacéuticamente aceptable del mismo.

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83. El compuesto del 80 indicado precedentemente, en donde R^3 y R^4 son iguales o diferentes y cada uno es

(1) un átomo de hidrógeno,

(2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más grupos hidroxilo),

(3) un grupo fenilo (dicho grupo fenilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de un átomo de halógeno y un grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más átomos halógenos), o

(4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros, o una sal farmacéuticamente aceptable del mismo.

84. El compuesto del 80 indicado precedentemente, o un farmacéuticamente de eso sal aceptable que se selecciona de lo siguiente:

(1) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-(3-piridin-3-il)pirrolidina,

(2) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-{(R)-3-(2-trifluorometilfenil)}pirrolidina,

(3) 1-{5-ciclopropil-1-[1-(1-metilciclopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-{(R)-3-(2-trifluorometilfenil)}pirrolidina,

(4) 1-{5-ciclopropil-1-[1-(1-isopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-{(R)-3-(2-trifluorometilfenil)}pirrolidina,

(5) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-{(S)-3-(2-trifluorometilfenil)}pirrolidina,

(6) 1-{5-ciclopropil-1-[1-(1-isopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-{(S)-3-(2-trifluorometilfenil)}pirrolidina,

(7) 1-{5-ciclopropil-1-[1-(1-metilciclopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-{(S)-3-(2-trifluorometilfenil)}pirrolidina,

(8) clorhidrato de (-)1-{5-(1-metilciclopropil)-1-[(1-pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(4-fluorofenil)-3-hidroximetilpirrolidina,

(9) clorhidrato de (+)1-{5-(1-metilciclopropil)-1-[(1-pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(4-fluorofenil)-3-hidroximetilpirrolidina,

(10) ácido 4-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoico,

(11) ácido 3-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoico,

(12) ácido 5-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiofen-2-carboxílico, y

(13) ácido 2-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiazol-4-carboxílico.

85. Una composición farmacéutica que comprende el compuesto de acuerdo con cualquiera de 80 a 84 indicados precedentemente, o una sal farmacéuticamente aceptable del mismo, y un vehículo farmacéuticamente aceptable.

86. Un inhibidor de 11βHSD1 que comprende el compuesto de acuerdo con cualquiera de 80 a 84 indicados precedentemente, o una sal farmacéuticamente aceptable del mismo, como ingrediente activo.

87. Un agente para el tratamiento o profilaxis de una patología que involucra glucocorticoide que comprende el compuesto de acuerdo con cualquiera de 80 a 84 indicados precedentemente, o una sal farmacéuticamente aceptable del mismo, como un ingrediente activo.

88. El agente del 87 indicado precedentemente, en donde la patología

que involucra glucocorticoide es

(1) una enfermedad metabólica que incluye diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión o hígado graso,

(2) un síndrome metabólico,

(3) un evento vascular fatal que incluye infarto cardiaco o apoplejía cerebral basada en tales enfermedades,

(4) hiperorexia,

(5) una enfermedad neurodisfuncional que incluye disgnosia, enfermedades neurodegenerativas acompañadas por desaparición de células nerviosas, desórdenes emocionales que incluyen ansiedad, depresión o manía, esquizofrenia o estímulo del apetito,

(6) una enfermedad que requiere tratamiento o profilaxis de inmunidad disminuida o aumento de inmunidad, incluyendo inmunodeficiencia,

(7) glaucoma, o

(8) osteoporosis.

89. La composición farmacéutica del 85 indicado precedentemente, a ser usada en combinación con 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

90. El inhibidor de 11βHSD1 del 86 indicado precedentemente, a ser usado en combinación con 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

91. El agente de acuerdo con 87 o 88 indicados precedentemente, el cual va a ser utilizado en combinación con 1 a 3 agentes seleccionados de los siguientes (1) a (5):

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas,

(5) un agente para el tratamiento o profilaxis de hipertensión.

92. La composición farmacéutica del 85 indicado precedentemente, que es usada para suprimir el incremento de nivel de glucocorticoide de la sangre utilizado en combinación con un agente farmacéutico que eleva el nivel de glucocorticoide de la sangre.

93. El inhibidor de 11βHSD1 del 86 indicado precedentemente, que es usado para suprimir el incremento de nivel de glucocorticoide de la sangre utilizado en combinación con un agente farmacéutico que eleva el nivel de glucocorticoide de la sangre.

MODALIDADES PREFERIDAS DE LA INVENCION

La presente invención será descrita en detalle a continuación.

En la presente invención, las definiciones de los sustituyentes a ser usados son las siguientes.

El "grupo alquilo de C_{1-6}" es un grupo alquilo de cadena lineal o ramificada que posee 1 a 6 átomos de carbono y, por ejemplo, se pueden indicar grupo metilo, grupo etilo, grupo propilo, grupo isopropilo, grupo butilo, grupo isobutilo, grupo sec-butilo, grupo ter-butilo, grupo pentilo, grupo isopentilo, grupo neopentilo, grupo ter-pentilo, grupo 1,2-dimetil-propilo, grupo hexilo, grupo 1,3-dimetil-butilo y lo similar, dando preferencia a un grupo alquilo de cadena lineal o ramificada que posee 1 a 4 átomos de carbono.

Para R^1, el "grupo alquilo de C_{1-6}" preferible es grupo metilo, grupo etilo, grupo isopropilo o grupo isobutilo.

Para R^3 o R^4, el "grupo alquilo de C_{1-6}" preferible es grupo metilo.

Para R^5 o R^6, el "grupo alquilo de C_{1-6}" preferible es grupo etilo, grupo isopropilo, grupo ter-butilo, grupo 1,2-dimetil-propilo o grupo 1,3-dimetil-butilo.

Para R^9, el "grupo alquilo de C_{1-6}" preferible es grupo metilo.

Para R^{10}, el "grupo alquilo de C_{1-6}" preferible es grupo metilo o grupo etilo.

Para R^{11}, el "grupo alquilo de C_{1-6}" preferible es grupo metilo, grupo etilo, grupo propilo, grupo isopropilo, grupo isobutilo o grupo ter-butilo.

Para R^{12}, el "grupo alquilo de C_{1-6}" preferible es grupo metilo o grupo

etilo.

Para R^{13}, el "grupo alquilo de C_{1-6}" preferible es grupo metilo.

Para R^{14} o R^{15}, el "grupo alquilo de C_{1-6}" preferible es grupo metilo.

El "grupo alquenilo C_{2-6}" es un grupo alquenilo de cadena lineal o ramificada que posee 2 a 6 átomos de carbono y, por ejemplo, se puede indicar grupo vinilo, grupo n-propenilo, grupo isopropenilo, grupo n-butenilo, grupo isobutenilo, grupo sec-butenilo, grupo ter-butenilo, grupo n-pentenilo, grupo isopentenilo, grupo neopentenilo, grupo 1-metilpropenilo, grupo n-hexenilo, grupo isohexenilo, grupo 1,1-dimetilbutenilo, grupo 2,2-dimetilbutenilo, grupo 3,3-dimetilbutenilo, grupo 3,3-dimetilpropenilo, grupo 2-etilbutenilo y lo similar.

El "grupo alcoxilo de C_{1-6}" es un grupo alcoxilo en donde la fracción alquilo es el "grupo alquilo de C_{1-6}" definido precedentemente y, por ejemplo, puede ser indicado grupo metoxilo, grupo etoxilo, grupo propoxilo, grupo isopropiloxilo, grupo butoxilo, grupo isobutiloxilo, grupo ter-butiloxilo, grupo pentiloxilo, grupo hexiloxilo y lo similar.

El "átomo halógeno" es átomo de flúor, átomo de cloro, átomo de bromo o átomo de yodo. El preferido es átomo de flúor o átomo de cloro y más preferido es el átomo de flúor.

El "grupo arilo" es un grupo hidrocarburo aromático que tiene 6 a 14 átomos de carbono y, por ejemplo, se puede indicar grupo fenilo, grupo naftilo, grupo antrilo, grupo azulenilo, grupo fenantrilo y lo similar. El preferido es grupo fenilo.

El "grupo ariloxilo" es un grupo ariloxilo en donde la fracción arilo es el "grupo arilo" definido precedentemente y, por ejemplo, se puede ejemplificar grupo fenoxilo, grupo naftiloxilo y lo similar.

El "grupo cicloalquilo" es un grupo cicloalquilo que posee 3 a 8 átomos

de carbono y, por ejemplo, se puede ejemplificar grupo ciclopropilo, grupo ciclobutilo, grupo ciclopentilo, grupo ciclohexilo, grupo cicloheptilo, grupo ciclooctilo y lo similar. Los preferibles son grupo cicloalquilo que posee 3 a 6 átomos de carbono, tal como grupo ciclopropilo, grupo ciclobutilo, grupo ciclopentilo y grupo ciclohexilo. Particularmente preferibles son grupo ciclopropilo y grupo ciclopentilo.

El "grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros" es un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros que posee, además del átomo de carbono, por lo menos uno, preferentemente 1 a 4, heteroátomos seleccionados del átomo de nitrógeno, átomo de oxígeno y átomo de azufre. La no saturación incluye insaturación parcial e insaturación completa. Por ejemplo, se puede indicar grupo heterocíclico monocíclico aromático de 5 miembros tal como grupo furilo, grupo tienilo, grupo pirrolilo, grupo pirazolilo, grupo imidazolilo, grupo oxazolilo, grupo isoxazolilo, grupo tiazolilo, grupo isotiazolilo, grupo triazolilo, grupo oxadiazolilo, grupo tetrazolilo, grupo tiadiazolilo y lo similar, y un grupo heterocíclico monocíclico aromático de 6 miembros tal como grupo piridilo, grupo piridazinilo, grupo pirimidinilo, grupo pirazinilo, grupo triazinilo, grupo tiazinilo, grupo oxadiazinilo, grupo piranilo, grupo tiopiranilo y lo similar. Como grupo heterocíclico monocíclico aromático de 5 miembros, el preferible es grupo tienilo o grupo tiazolilo. Como grupo heterocíclico monocíclico aromático de 6 miembros, el preferible es grupo piridilo o grupo pirimidinilo.

Para R^1, el "grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros preferible es grupo piridilo, grupo tienilo, grupo tiazolilo, grupo triazolilo (particularmente preferiblemente grupo 1,2,4-triazolilo), grupo tetrazolilo, grupo pirimidinilo o grupo pirazinilo.

Para R^3 ó R^4, el "grupo heterocíclico monocíclico no saturado de 5

miembros ó de 6 miembros" preferible es grupo piridilo o grupo tiazolilo. Más preferible es grupo piridilo.

El "grupo heterocíclico monocíclico saturado que contiene nitrógeno es, por ejemplo, un heterociclo monocíclico saturado de 4 miembros a 6 miembros que posee por lo menos un átomo de nitrógeno, tal como grupo azetidinilo, grupo pirrolidinilo, grupo imidazolidinilo, grupo pirazolidinilo, grupo oxazolidinilo, grupo 2-oxopirrolidinilo, grupo tiazolidinilo, grupo isotiazolidinilo, grupo piperidilo, grupo piperazinilo, grupo morfolinilo, grupo tiomorfolinilo, grupo 2-oxopiperidinilo, grupo 4-oxopiperidinilo, grupo 2,6-dioxopiperidinilo y lo similar.

El "grupo heterocíclico monocíclico saturado que contiene nitrógeno" preferible es grupo azetidinilo, grupo pirrolidinilo, grupo piperidilo, grupo piperazinilo o grupo tiomorfolinilo.

Para $-NR^5R^6$, el "grupo heterocíclico monocíclico saturado que contiene nitrógeno" preferible es grupo azetidinilo, grupo pirrolidinilo, grupo piperidilo, grupo piperazinilo o grupo tiomorfolinilo (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

átomo halógeno,

grupo hidroxilo,

grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más grupos hidroxilo,

grupo carboxilo,

grupo acetilo,

grupo carbamoilo,

grupo amino opcionalmente sustituido con uno o más sustituyentes

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iguales o diferentes seleccionados del grupo alquilo de C_{1-6} y grupo acetilo, y grupos oxo).

Para $-NR^{20}R^{21}$, el "grupo heterocíclico monocíclico saturado que contiene nitrógeno" preferible es grupo azetidinilo, grupo pirrolidinilo o grupo piperidilo (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del átomo halógeno y grupo hidroxilo).

Para $-NR^{26}R^{27}$, el "grupo heterocíclico monocíclico saturado que contiene nitrógeno" preferible es grupo piperidilo o grupo pirrolidinilo, más preferentemente grupo piperidilo.

Para R^{10}, el grupo heterocíclico monocíclico saturado que contiene nitrógeno" preferible es grupo piperidilo.

Para R^{11}, el "grupo heterocíclico monocíclico saturado que contiene nitrógeno" preferible es grupo pirrolidinilo o grupo piperidilo (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo alquilo de C_{1-6}, grupo -CO-alquilo de C_{1-6} y grupo oxo).

El significado de "opcionalmente sustituido con uno o más sustituyentes" implica sin sustituir u opcionalmente sustituido por lo menos con uno al número máximo aceptable de sustituyentes. Por ejemplo, en el caso de grupo metilo, significa que es opcionalmente sustituido con 1 a 3 sustituyentes, y en el caso de grupo etilo, significa que es opcionalmente sustituido con 1 a 5 sustituyentes. Los sustituyentes en el caso de substitución con dos o más sustituyentes pueden ser iguales o diferentes y no están limitados particularmente a posiciones de sustituyentes y pueden ser de cualquier posición.

El "grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más, sustituyentes iguales o diferentes" es preferentemente grupo alquilo de C_{1-6}

opcionalmente sustituido con 1 a 3 sustituyentes iguales o diferentes. Particularmente, el "grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes" es preferentemente grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos halógenos, más preferentemente un grupo alquilo de C_{1-6} opcionalmente sustituido con tres átomos halógenos, y más preferentemente grupo trifluorometilo o grupo 2,2,2-trifluoroetilo.

Los grupos preferibles de cada grupo son los siguientes.

Anillo A preferible

Anillo A es

(1) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (es decir, -X- es $-N(R^1)-$), o

(2) un grupo cicloalquilo (es decir, -X- es $-C(R^7R^8)-$), y preferentemente

(1) un grupo azetidinilo o un grupo piperidilo, o

(2) un grupo ciclohexilo.

R^2 preferible

R^2 es preferentemente un grupo ciclopropilo o un grupo ciclohexilo opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con un grupo hidroxilo) y un grupo alcoxilo de C_{1-6}. Más preferentemente, es un grupo ciclopropilo o un grupo ciclohexilo opcionalmente sustituido con uno o más grupos metilo (dicho grupo metilo es opcionalmente sustituido con un grupo hidroxilo) o grupos metoxilo. Particularmente preferentemente, es grupo ciclopropilo, grupo metilciclopropilo, grupo metoxiciclopropilo, grupo tetrametilciclopropilo, grupo hidroximetilciclopropilo o grupo ciclohexilo.

R^3 y R^4 preferibles

R^3 y R^4 no son preferentemente átomos de hidrógeno al mismo tiempo.

Más preferentemente, uno de R^3 y R^4 es un átomo de hidrógeno, un grupo hidroxilo, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del átomo halógeno, grupo hidroxilo, grupo metoxilo y grupo acetiloxilo) o un grupo alcoxilo de C_{1-6}, y el otro no es un átomo de hidrógeno.

Aún más preferiblemente, uno de R^3 y R^4 es un átomo de hidrógeno, un grupo hidroxilo, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del átomo halógeno, grupo hidroxilo, grupo metoxilo y grupo acetiloxilo) o un grupo alcoxilo de C_{1-6}, y el otro es un sustituyente seleccionado del grupo siguiente, el cual es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del átomo halógeno, grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más, átomos halógenos iguales o diferentes o grupo hidroxilo), grupo alcoxilo de C_{1-6} (dicho grupo alcoxilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), grupo alcoxicarbonilo C_{1-6} y grupo ciano:

grupo fenilo,

piridilo grupo, y

grupo tiazolilo.

Particularmente preferentemente, uno de R^3 y R^4 es un átomo de hidrógeno, un grupo hidroxilo, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del átomo halógeno, grupo hidroxilo, grupo metoxilo y grupo acetiloxilo) o un grupo metoxilo, y

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el otro es un sustituyente seleccionado del grupo siguiente, el cual es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del átomo halógeno, grupo trifluorometilo, grupo trifluorometoxilo, grupo metoxicarbonilo, grupo hidroximetilo y grupo ciano:

grupo fenilo,

grupo piridilo, y

grupo tiazolilo.

R^5 y R^6 preferibles

R^5 y R^6 son preferentemente iguales o diferentes y cada uno es

un átomo de hidrógeno,

un grupo fenilo opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo hidroxilo, átomo halógeno, grupo carboxilo y grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más grupos hidroxilo o átomos halógenos),

un grupo cicloalquilo que posee 3 a 6 átomos de carbono (dicho grupo cicloalquilo es opcionalmente sustituido por un grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más grupos hidroxilo),

un grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo hidroxilo, átomo halógeno, grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por átomo halógeno), el grupo carboxilo y el $-NR^{20}R^{21}$ (en donde R^{20} y R^{21} son iguales a los definidos para la fórmula [1]),

$-S(=O)_2-R^9$ en donde R^9 es grupo fenilo o grupo alquilo de C_{1-6},

grupo alcoxilo de C_{1-6} opcionalmente sustituido,

grupo piridinilo opcionalmente sustituido con átomo halógeno en la

posición 2 y posición 6,

un grupo heterocíclico no saturado que contiene nitrógeno opcionalmente sustituido, o

un grupo heterocíclico monocíclico saturado que contiene nitrógeno opcionalmente sustituido con uno o más sustituyentes iguales o diferentes, seleccionados del grupo alquilo de C_{1-6} y grupo -CO-alquilo de C_{1-6}, o

R^5 y R^6 pueden formar, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno seleccionado del grupo azetidinilo, grupo pirrolidinilo, grupo piperidilo, grupo piperazinilo, y grupo tiomorfolinilo, o un grupo heterocíclico seleccionado del grupo dihidroindolilo, grupo dihidro[1,4]oxazinilo, y grupo tetrahidrobenzo[b]azepinilo, el cual es un anillo fusionado de dicho heterociclo y un anillo de carbono (ambos grupos heterocíclicos mencionados son opcionalmente sustituidos con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

átomo halógeno,

grupo hidroxilo,

grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más grupos hidroxilo,

grupo carboxilo,

grupo acetilo,

grupo carbamoilo,

grupo amino opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo alquilo de C_{1-6} y grupo acetilo, y

grupo oxo).

Más preferentemente, R^5 y R^6 son iguales o diferentes y cada uno es

un átomo de hidrógeno,

un grupo fenilo opcionalmente sustituido en posición orto y/o posición para por sustituyentes seleccionados del grupo hidroxilo, átomo halógeno, grupo carboxilo y grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más grupos hidroxilo o átomos halógenos),

un grupo ciclopropilo o un grupo ciclopentilo opcionalmente sustituido con grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más grupos hidroxilo,

un grupo alquilo de C_{1-6} sustituido con uno o más sustituyentes iguales o diferentes, seleccionados del grupo hidroxilo, átomo halógeno, grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por átomo halógeno), grupo carboxilo y -$NR^{20}R^{21}$ (en donde R^{20} y R^{21} son iguales a los definidos para la fórmula [1]),

-$S(=O)_2$-R^9 en donde R^9 es un grupo fenilo o un grupo metilo,

un grupo alcoxilo de C_{1-6},

un grupo piridinilo sustituido con átomo halógeno en la posición 2 y la posición 6,

un grupo tiazolilo opcionalmente sustituido, o

un grupo piperidin-4-ilo opcionalmente sustituido en la posición 1 con un sustituyente seleccionado del grupo alquilo de C_{1-6} y grupo -CO-alquilo de C_{1-6}, o

R^5 y R^6 pueden formar, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno seleccionado del grupo azetidin-1-ilo, grupo pirrolidin-1-ilo, grupo piperidin-1-ilo, grupo piperazin-1-ilo, y grupo tiomorfolin-4-ilo, o un grupo heterocíclico seleccionado del grupo dihidroindol-1-ilo, grupo dihidro[1,4]oxazin-1-ilo, y grupo tetrahidrobenzo[b]azepin-1-ilo el cual es un anillo fusionado de dicho heterociclo y un anillo de carbono (ambos grupos heterocíclicos mencionados son opcionalmente

sustituidos con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

átomo halógeno,

grupo hidroxilo,

grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más grupos hidroxilo,

grupo carboxilo,

grupo acetilo,

grupo carbamoilo,

grupo amino opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo alquilo de C_{1-6} y grupo acetilo, y

grupo oxo).

Aún más preferiblemente, R^5 y R^6 son iguales o diferentes y cada uno es

un átomo de hidrógeno,

un grupo fenilo sustituido en posición orto y/o posición para por sustituyentes seleccionados del grupo hidroxilo, átomo halógeno, grupo carboxilo y grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más grupos hidroxilo o átomos halógenos),

un grupo ciclopropilo o un grupo ciclopentilo sustituidos por grupo alquilo de C_{1-6} sustituido con uno o más grupos hidroxilo,

un grupo alquilo de C_{1-6} sustituido por un sustituyente seleccionado del grupo hidroxilo, átomo halógeno, grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por átomo halógeno), grupo carboxilo y $-NR^{20}R^{21}$ (en donde R^{20} y R^{21} son iguales a los definidos para la fórmula [1]),

$-S(=O)_2-R^9$ en donde R^9 es un grupo fenilo o un grupo metilo,

un grupo alcoxilo de C_{1-6},

un grupo piridin-3-ilo sustituido con átomo halógeno en la posición 2 y la posición 6,

un grupo tiazolilo, o

un grupo piperidin-4-ilo opcionalmente sustituido en la posición 1 con un grupo -CO-alquilo de C_{1-6}, o

R^5 y R^6 pueden formar, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico de monocíclico saturado que contiene nitrógeno seleccionado del grupo azetidin-1-ilo, grupo pirrolidin-1-ilo, piperidin-1-ilo, grupo piperazin-1-ilo, y grupo tiomorfolin-4-ilo, o un grupo heterocíclico seleccionado del grupo dihidroindol-1-ilo, grupo dihidro[1,4]oxazin-1-ilo, y grupo tetrahidrobenzo[b]azepin-1-ilo, el cual es un anillo fusionado de dicho heterociclo y un anillo de carbono (ambos grupos heterocíclicos mencionados son opcionalmente sustituidos con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente:

átomo halógeno,

grupo hidroxilo,

grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más grupos hidroxilo,

grupo carboxilo,

grupo acetilo,

grupo carbamoilo,

grupo amino opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo alquilo de C_{1-6} y grupo acetilo, y

grupo oxo).

Particularmente preferentemente, R^5 y R^6 son iguales o diferentes y cada uno es

átomo de hidrógeno,

grupo 2-fluorofenilo,

grupo 2-carboxifenilo,

grupo 2-hidroximetilfenilo,

grupo 1-hidroximetilciclopropilo,

grupo 2-hidroxiletilo,

grupo 2-hidroxi-1,1-dimetiletilo,

grupo 2-acetilaminoetilo,

grupo 2-aminoetilo,

grupo 2-dimetilaminoetilo,

grupo 2-piperidin-1-il-etilo,

grupo 2-hidroxi-1-metiletilo,

grupo piperidin-4-ilo,

grupo 1-metil-piperidin-4-ilo,

grupo 1-acetil-piperidin-4-ilo,

grupo 2,2,2-trifluoroetilo,

grupo 1-hidroximetil-2-metilpropilo,

grupo 1-hidroximetil-2-feniletilo,

grupo 2-hidroxi-1-feniletilo,

grupo 1-hidroximetil-3-metilbutilo,

grupo 2-hidroxifenilo,

grupo 1-hidroximetil-ciclopentilo,

grupo bencensulfonilo,

grupo 4-trifluorometilfenilo,

grupo 2,4-difluorofenilo,

grupo 1-carboxi-2-metilpropilo,

grupo tiazol-2-ilo,

grupo isopropoxilo,

grupo 4-fluorobencilo,

grupo 2,6-dicloropiridin-3-ilo,

grupo etoxilo, o

grupo mesilo, o

R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno o un grupo heterocíclico que es un anillo fusionado de dicho heterociclo y un anillo de carbono que se selecciona del grupo siguiente:

grupo azetidin-1-ilo,

grupo 3-hidroxiazetidin-1-ilo,

grupo 3-hidroximetilazetidin-1-ilo,

grupo 3-acetilazetidin-1-ilo,

grupo 3-acetilaminoazetidin-1-ilo,

grupo 3-hidroxipirrolidin-1-ilo,

grupo 3,3-difluoropirrolidin-1-ilo,

grupo 3,3,4,4-tetrafluoropirrolidin-1-ilo,

grupo 2-hidroximetilpirrolidin-1-ilo,

grupo 2-aminopirrolidin-1-ilo,

grupo 2-acetilaminopirrolidin-1-ilo,

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grupo 2-dimetilaminopirrolidin-1-ilo,

grupo 3-oxo-pirrolidin-1-ilo,

grupo 4-hidroxipiperidin-1-ilo,

grupo 4,4-difluoropiperidin-1-ilo,

grupo 4-hidroximetilpiperidin-1-ilo,

grupo 4-carboxipiperidin-1-ilo,

grupo 3-hidroxipiperidin-1-ilo,

grupo 4-carbamoilpiperidin-1-ilo,

grupo 4-aminopiperidin-1-ilo,

grupo 4-dimetilaminopiperidin-1-ilo,

grupo 4-acetilaminopiperidin-1-ilo,

grupo 4-metilpiperazin-1-ilo,

grupo 4-isopropilpiperazin-1-ilo,

grupo 4-acetilpiperazin-1-ilo,

grupo 1,1-dioxotiomorfolin-4-ilo,

grupo 3-oxo-piperidin-1-ilo,

grupo 4-oxo-piperidin-1-ilo,

grupo 2,3-dihidroindol-1-ilo,

grupo 2,3-dihidro[1,4]oxazin-1-ilo, y

grupo 2,3,4,5-tetrahidrobenzo[b]azepin-1-ilo.

Aún más preferiblemente, R^5 y R^6 no son al mismo tiempo átomos de hidrógeno. Más preferentemente, uno de R^5 y R^6 es un átomo de hidrógeno y el otro no es un átomo de hidrógeno.

R^{10} preferible

R^{10} es preferentemente

un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo hidroxilo, grupo fenilo y $-NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman un grupo piperidilo junto con el átomo de nitrógeno unido a los mismos), o

un grupo piperidilo (dicho grupo piperidilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo alquilo de C_{1-6} y grupo -CO-alquilo de C_{1-6}).

R^{10} es más preferentemente

un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo hidroxilo, grupo fenilo y $-NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es el grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman un grupo piperidilo junto con el átomo de nitrógeno unido a los mismos), o

un grupo piperidin-4-ilo (dicho grupo piperidin-4-ilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo alquilo de C_{1-6} y grupo -CO-alquilo de C_{1-6}).

R^{10} es preferentemente

un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más iguales o diferentes sustituyentes seleccionados del grupo hidroxilo, grupo fenilo y $-NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman un grupo piperidilo junto con el átomo de nitrógeno unido a los mismos), o

un grupo piperidin-4-ilo (dicho grupo piperidin-4-ilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo

alquilo de C_{1-6} y grupo -CO-alquilo de C_{1-6}).

R^{10} es particularmente preferentemente

grupo metilo,

grupo 2-hidroxiletilo,

grupo 2-dimetilaminoetilo,

grupo 2-piperidin-1-il-etilo,

grupo piperidin-4-ilo,

grupo 1-metil-piperidin-4-ilo,

grupo bencilo, o

grupo 1-acetil-piperidin-4-ilo.

R^{11} preferible

R^{11} es preferentemente

un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al g):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o grupo $-S(=O)_2$-alquilo de C_{1-6},

d) un grupo carbamoilo,

e) un grupo carboxilo.

f) un grupo fenoxilo, y

g) un grupo fluorofenil).

un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente

sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b):

a) un grupo arilo opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes, y.

b) un grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más grupos hidroxilo),

un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c)..:

a) uno o más átomos halógenos iguales o diferentes.

b) un grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes, y

c) un grupo alcoxilo de C_{1-6}).

un grupo carboxilo, o

un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6}.

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo).

R^{11} es más preferentemente

un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al g):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es

un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o grupo -$S(=O)_2$-alquilo de C_{1-6}.

d) un grupo carbamoilo,

e) un grupo carboxilo,

f) un grupo fenoxilo, y

g) un grupo fluorofenilo),

un grupo ciclopropilo (dicho grupo ciclopropilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b):

a) un grupo arilo opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes, y

b) un grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más grupos hidroxilo),

un grupo fenilo (dicho grupo fenilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) uno o más átomos halógenos iguales o diferentes.

b) un grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes, y

c) un grupo alcoxilo de C_{1-6}).

un grupo carboxilo, o

un grupo heterocíclico monocíclico saturado que contiene nitrógeno seleccionado de un grupo pirrolidinilo y un grupo piperidilo (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): .

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo).

R^{11} es preferentemente además

un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al g):

a) un átomo de halógeno,

b) un grupo hidroxilo,

c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o grupo $-S(=O)_2$-alquilo de C_{1-6},

d) un grupo carbamoilo,

e) un grupo carboxilo,

f) un grupo fenoxilo, y

g) un grupo fluorofenilo),

un grupo ciclopropilo (dicho grupo ciclopropilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b):

a) un grupo arilo opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes, y

b) un grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más grupos hidroxilo),

un grupo fenilo (dicho grupo fenilo es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) uno o más átomos halógenos iguales o diferentes,

b) un grupo alquilo de C_{1-6} opcionalmente sustituido con uno o más

átomos halógenos iguales o diferentes, y

c) un grupo alcoxilo de C_{1-6}),

un grupo carboxilo, o

un grupo heterocíclico monocíclico saturado que contiene nitrógeno seleccionado de un grupo pirrolidin-2-ilo y un grupo piperidin-4-ilo (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c):

a) un grupo alquilo de C_{1-6},

b) un grupo -CO-alquilo de C_{1-6}, y

c) un grupo oxo).

R^{11} es particularmente preferentemente

grupo 2,2,2-trifluoroetilo,

grupo hidroximetilo,

grupo 3-hidroxipropilo,

grupo 2-hidroxi-1,1-dimetil-etilo,

grupo aminometilo,

grupo 2-amino-etilo,

grupo 1-amino-1-metil-etilo,

grupo 1-amino-2-metil-propilo.

grupo metilamino-metilo,

grupo dimetilamino-metilo,

grupo acetilamino-metilo,

grupo 1-acetilamino-etilo,

grupo 2-acetilamino-etilo,

grupo 1-acetilamino-1-metil-etilo.

grupo 1-acetilamino-2-metil-propilo,

grupo isobutirilamino-metilo,

grupo ciclopropancarbonil-amino-metilo,

grupo metansulfonilamino-metilo,

grupo 2-carbamoil-etilo,

grupo ciclopropilo,

grupo 1-(4-fluoro-fenil)-ciclopropilo,

grupo 1-metil-ciclopropilo,

grupo 1-hidroximetil-ciclopropilo,

grupo pirrolidin-1-ilo,

grupo pirrolidin-2-ilo,

grupo piperidin-4-ilo,

grupo 1-metil-pirrolidin-2-ilo,

grupo 1-metil-piperidin-4-ilo,

grupo 1-acetil-pirrolidin-2-ilo,

grupo 1-acetil-piperidin-4-ilo,

grupo 2-carboxi-2-metilpropilo,

grupo fenoximetilo,

grupo 2-clorofenilo,

grupo 3-clorofenilo,

grupo 4-clorofenilo,

grupo carboxilo,

grupo 4-fluorobencilo,

grupo 3-trifluorometilfenilo,

grupo 3-metoxifenilo, o

grupo 5-oxo-pirrolidin-2-ilo.

La sal del compuesto de la presente invención es preferentemente una sal farmacéuticamente aceptable. La sal del compuesto de la presente invención representada por la fórmula [1'] puede ser producido por medio de un método convencional. La sal del compuesto de la presente invención representada por la fórmula [1'] se puede obtener haciendo reaccionar el compuesto [1'] (más adelante en la presente, el compuesto [1'] y las sales de los mismos también son denominadas colectivamente el compuesto de la presente invención) con, por ejemplo, ácidos inorgánicos tales como ácido clorhídrico, ácido sulfúrico, ácido fosfórico, ácido bromhídrico y lo similar; ácidos orgánicos tales como ácido oxálico, ácido malónico, ácido cítrico, ácido fumárico, ácido láctico, ácido málico, ácido succínico, ácido tartárico, ácido acético, ácido glucónico, ácido trifluoracético, ácido ascórbico, ácido metansulfónico, ácido bencensulfónico y lo similar; las bases inorgánicas tales como hidróxido de sodio, hidróxido de potasio, hidróxido de calcio, hidrato de magnesio, hidróxido de amonio y lo similar; las bases orgánicas tales como metilamina, dietilamina, trietilamina, trietanolamina, etilenediamina, tris(hidroximetil)metilamina, guanidina, colina, cinconina y lo similar; los aminoácidos tales como lisina, arginina, alanina y lo similar, y lo similar. La presente invención también abarca los productos que contienen agua, hidratos y solvatos del compuesto de la presente invención.

Adicionalmene, el compuesto de la presente invención tiene varios isómeros. Por ejemplo, la forma E y forma Z pueden estar presentes como isómeros geométricos, cuando un átomo de carbono asimétrico está presente, los enantiómeros y diaestereómeros están presentes como estereoisómeros basados en el mismo, y los tautómeros también pueden estar presentes. Por consiguiente, la presente invención abarca todos estos isómeros y mezclas de los mismos. Además,

la presente invención abarca, además del compuesto de la presente invención, los compuestos profármaco y compuestos metabolitos de estos compuestos así como los compuestos equivalentes.

Tal como es utilizado en la presente, "profármaco" es un derivado que posee un grupo que puede ser descompuesto químicamente o metabólicamente que demuestra una actividad farmacéutica en la descomposición por hidrólisis o solvólisis o bajo condiciones fisiológicas. Por ejemplo, un profármaco es utilizado para mejorar la absorción por administración oral o alcanzar el sitio objetivo. Ya que el grupo que puede ser descompuesto químicamente o metabólicamente, y la modalidad en la cual el grupo es introducido en un compuesto ha sido suficientemente establecida en el campo de los agentes farmacéuticos, tales técnicas conocidas se pueden emplear en la presente invención. Como la fracción a ser modificada para producir un profármaco, por ejemplo, se pueden indicar los grupos funcionales altamente reactivos tales como grupo hidroxilo, grupo carboxilo, grupo amino, grupo tiol y lo similar en el compuesto de la presente invención.

Por ejemplo, se puede indicar un derivado en donde un sustituyente tal como un grupo -CO-alquilo de C_{1-6}, grupo -CO_2-alquilo de C_{1-6}, grupo -CONH-alquilo de C_{1-6}, grupo -CO-alquenilo de C_{2-6}, grupo -CO_2-alquenilo de C_{2-6}, grupo -CONH-alquenilo de C_{2-6}, grupo -CO-arilo, grupo -CO_2-arilo, grupo -CONH-arilo, grupo -CO-heterocíclico, grupo -CO_2-heterocíclico, grupo -CONH-heterocíclico (grupo alquilo de C_{1-6}, grupo alquenilo de C_{2-6}, grupo arilo y grupo heterocíclico son opcionalmente cada uno sustituido con átomo halógeno, grupo alquilo de C_{1-6}, grupo hidroxilo, grupo alcoxilo C_{1-6}, grupo carboxilo, grupo amino, residuo de aminoácido, -PO_3H_2, -SO_3H, residuo de -CO-polietilénglicol, residuo de -CO_2-polietilenglicol, residuo de -CO-polietilénglicol monoalquil éter, un residuo de -CO_2-polietilén glicol monoalquil éter y

lo similar) y lo similar se ha introducido en un grupo hidroxilo.

Adicionalmene, se puede indicar un derivado en donde un sustituyente como grupo -CO-alquilo de C_{1-6}, grupo -CO_2-alquilo de C_{1-6}, grupo -CO-alquenilo de C_{2-6}, grupo -CO_2-alquenilo de C_{2-6}, grupo -CO-arilo, grupo -CO_2-arilo, grupo -CO-heterocíclico, grupo -CO_2-heterocíclico (grupo alquilo de C_{1-6}, grupo alquenilo de C_{2-6}, grupo arilo y grupo heterocíclico son opcionalmente sustituidos cada uno con átomo halógeno, grupo alquilo de C_{1-6}, grupo hidroxilo, grupo alcoxilo de C_{1-6}, grupo carboxilo, grupo amino, residuo de aminoácido, -PO_3H_2, -SO_3H, residuo de -CO-polietilen glicol, residuo de -CO_2-polietilén glicol, residuo de -CO-polietilén glicol monoalquil éter, residuo de -CO_2-polietilen glicol monoalquil éter, -PO_3H_2 y lo similar) y lo similar puede ser introducido en un grupo amino.

Además, se puede indicar un derivado en donde un sustituyente tal como grupo alcoxilo de C_{1-6}, grupo ariloxilo (grupo alcoxilo de C_{1-6} y grupo ariloxilo cada uno es opcionalmente sustituido con átomo halógeno, grupo alquilo de C_{1-6}, grupo hidroxilo, grupo alcoxilo de C_{1-6}, grupo carboxilo, grupo amino, residuo de aminoácido, -PO_3H_2, -SO_3H, residuo de polietilén glicol, residuo de polietilén glicol monoalquil éter y lo similar) y lo similar ha sido introducido en un grupo carboxilo.

En lo anterior, el "grupo heterocíclico" es un grupo heterocíclico monocíclico (incluyendo insaturación parcial e insaturación completa) de 5 miembros ó de 6 miembros saturado o no saturado que posee, además del átomo de carbono, por lo menos uno, preferentemente 1 a 4, heteroátomos seleccionados del átomo de nitrógeno, átomo de oxígeno y átomo de azufre, o un grupo en anillo fusionado de los heterociclos o un grupo en anillo fusionado del heterociclo y un anillo de carbono seleccionado del benceno, ciclopentano y hexametileno.

Como el "grupo heterocíclico monocíclico saturado de 5 miembros ó de

6 miembros", por ejemplo, se puede indicar grupo pirrolidinilo, grupo tetrahidrofurilo, grupo tetrahidrotienilo, grupo imidazolidinilo, grupo pirazolidinilo, grupo 1,3-dioxolanilo, grupo 1,3-oxatioranilo, grupo oxazolidinilo, grupo tiazolidinilo, grupo piperidinilo, grupo piperazinilo, grupo tetrahidropiranilo, grupo tetrahidrotiopiranilo, grupo dioxanilo, grupo morfolinilo, grupo tiomorfolinilo, grupo 2-oxopirrolidinilo, grupo 2-oxopiperidinilo, grupo 4-oxopiperidinilo, grupo 2,6-dioxopiperidinilo y lo similar.

Como el "grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros", por ejemplo, se puede indicar grupo pirrolilo, grupo furilo, tienilo grupo, grupo imidazolilo, grupo 1,2-dihidro-2-oxoimidazolilo, grupo pirazolilo, grupo diazolilo, grupo oxazolilo, grupo isoxazolilo, tiazolilo grupo, grupo isotiazolilo, grupo triazolilo (grupo 1,2,4-triazolilo, grupo 1,2,3-triazolilo), grupo tetrazolilo, grupo 1,3,4-oxadiazolilo, grupo 1,2,4-oxadiazolilo, grupo 1,3,4-tiadiazolilo, grupo 1,2,4-tiadiazolilo, grupo furazanilo, grupo piridilo, grupo pirimidinilo, grupo 3,4-dihidro-4-oxopirimidinilo, grupo piridazinilo, grupo pirazinilo, grupo 1,3,5-triazinilo, grupo imidazolinilo, grupo pirazolinilo, grupo oxazolinilo (grupo 2-oxazolinilo, grupo 3-oxazolinilo, grupo 4-oxazolinilo), grupo isooxazolinilo, grupo tiazolinilo, grupo isotiazolinilo, grupo piranilo, grupo 2-oxopiranilo, grupo 2-oxo-2,5-dihidrofuranilo y grupo 1,1-dioxo-1H-isotiazolilo.

Como el "grupo heterocíclico que es un anillo fusionado", por ejemplo, se puede indicar grupo indolilo (por ejemplo, grupo 4-indolilo, grupo 7-indolilo, etc.), grupo isoindolilo, grupo 1,3-dihidro-1,3-dioxoisoindolilo, grupo benzofuranilo (por ejemplo, grupo 4-benzofuranilo, grupo 7-benzofuranilo etc.), grupo indazolilo, grupo isobenzofuranilo, grupo benzotiofenilo (por ejemplo, grupo 4-benzotiofenilo, grupo 7-benzotiofenilo, etc.), grupo benzooxazolilo (por ejemplo, grupo 4-benzooxazolilo, grupo 7-benzooxazolilo etc.), grupo bencimidazolilo (por ejemplo, grupo 4-bencimidazolilo, grupo 7-bencimidazolilo etc.), grupo benzotiazolilo (por ejemplo,

grupo 4-benzotiazolilo, grupo 7-benzotiazolilo etc.), grupo indolizinilo, grupo quinolilo, grupo isoquinolilo, grupo 1,2-dihidro-2-oxoquinolilo, grupo quinazolinilo, grupo quinoxalinilo, grupo cinnolinilo, grupo ftalazinilo, grupo quinolizinilo, grupo purilo, grupo pteridinilo, grupo indolinilo, grupo isoindolinilo, grupo 5,6,7,8-tetrahidroquinolilo, grupo 1,2,3,4-tetrahidroquinolilo, grupo 2-oxo-1,2,3,4-tetrahidroquinolilo grupo, grupo benzo[1,3]dioxolilo, grupo 3,4-metilendioxipiridilo, grupo 4,5-etilendioxipirimidinilo, grupo cromenilo, grupo cromanilo, grupo isocromanilo y lo similar.

La "composición farmacéutica" incluye, además de lo que se denomina una "composición" que comprende un ingrediente activo tal como un agente farmacéutico y un medicamento de combinación y lo similar, un agente de combinación con otro fármaco, y lo similar. Es innecesario decir que la composición farmacéutica de la presente invención puede ser usada concurrentemente con cualquier otro fármaco dentro del rango aceptable en situaciones clínicas. Por consiguiente, la presente composición farmacéutica también puede ser considerada una composición farmacéutica a ser combinada con otro fármaco.

Además, la composición farmacéutica de la presente invención no sólo puede ser administrada a seres humanos sino también a otros mamíferos (ratón, rata, marmota, conejo, gato, perro, bovino, equino, oveja, mono, etc.). Por consiguiente, la composición farmacéutica de la presente invención también es útil como un producto farmacéutico para animales, sin mencionar al ser humano.

El compuesto de la presente invención o una sal del mismo puede ser mezclado con un vehículo farmacéuticamente aceptable, y es administrado oralmente o parenteralmente como tableta, píldora, polvo, gránulo, supositorio, inyección, colirio, líquido, cápsula, pastilla, aerosol, elixir, suspensión, emulsión, jarabe y lo similar.

Como "el vehículo farmacéuticamente aceptable", se pueden utilizar diversas sustancias de vehículo orgánicas o inorgánicas convencionalmente usadas como materiales de preparación, las cuales son agregadas como vehículo, lubricante, aglomerante, desintegrador, solvente, auxiliar de disolución, agente de suspensión, agente de isotonización, agente colorante, anestesia y lo similar. Cuando sea necesario, aditivos de preparación tales como conservador, antioxidante, agente colorante, agente edulzante y lo similar también pueden ser utilizados. Como los ejemplos del vehículo indicado precedentemente, puede mencionarse lactosa, sacarosa, D-manitol, almidón, celulosa cristalina, anhídrido silícico ligero y lo similar. Como lubricante indicado precedentemente, por ejemplo, puede mencionarse estearato de magnesio, estearato de calcio, talco, sílice coloidal y lo similar. Como los ejemplos de aglomerante indicado precedentemente, pueden mencionarse compuestos de polímero tales como celulosa cristalina, sacarosa, D-manitol, dextrina, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, polivinilpirrolidona y lo similar. Como los ejemplos del desintegrador indicado precedentemente, puede indicarse almidón, carboximetilcelulosa, carboximetilcelulosa de calcio, croscaramelosa, carboximetil de sodio, almidón de sodio y lo similar puede mencionarse. Como los ejemplos del solvente indicado precedentemente, se puede indicar agua para inyección, alcohol, propilenglicol, macrogol, aceite de sésamo, aceite de maíz, propilenglicol ésteres de ácidos grasos y lo similar. Como los ejemplos de auxiliares de disolución indicados precedentemente, puede mencionarse polietilen glicol, propilenglicol, D-manitol, benzoato de bencilo, etanol, trisaminometano, colesterol, trietanolamina, carbonato de sodio, citrato de sodio y lo similar. Como los ejemplos del agente de suspensión indicado precedentemente, se pueden indicar agentes tensioactivos tales como trietanolamina esteárica, sulfato de lauril sodio, ácido de lauril aminopropiónico,

lecitina, cloruro de benzalconio, cloruro de benzetonio, monostearato de glicerilo y lo similar; polivinil alcohol, polivinilpirrolidona, carboximetilcelulosa de sodio, metilcelulosa, hidroximetilcelulosa y lo similar. Como los ejemplos del agente de isotonización indicado precedentemente, se puede indicar cloruro de sodio, glicerol, D-manitol y lo similar. Como los ejemplos del amortiguador indicado precedentemente, pueden indicarse amortiguadores tales como fosfato, acetato, carbonato, citrato y lo similar, y lo similar. Como los ejemplos del agente de anestesiado indicado precedentemente, puede mencionarse alcohol bencílico y lo similar. Como los ejemplos de conservador indicado precedentemente, puede mencionarse paraoxibenzoatos, clorobutanol, alcohol bencílico, fenetil alcohol, ácido sórbico, ácido deshidroacético y lo similar. Como los ejemplos del antioxidante indicado precedentemente, puede mencionarse sulfito, ácido ascórbico y lo similar. Como los ejemplos del agente edulcorante indicado precedentemente, puede mencionarse aspartamo, sacarina de sodio, estevia y lo similar. Como los ejemplos del agente colorante indicado precedentemente, pueden indicarse colorantes comestibles tal como el Color Comestible Amarillo No. 5, Color Comestible Rojo No. 2 y Color Comestible Azul No. 2 y lo similar, color en laca comestible, óxido de hierro y lo similar.

El "inhibidor de 11βHSD1" significa desaparición o atenuación de la actividad de 11βHSD1 por inhibición específica de la función de la misma como una enzima, y significa, por ejemplo, la inhibición especifica de la función de 11βHSD1 bajo las condiciones del ejemplo Experimental 1 indicado más adelante, y preferentemente significa la concentración necesaria para lograr el 50% de inhibición de 11βHSD1 bajo las condiciones del ejemplo Experimental 1 indicado más adelante de menos de 10 μM, preferentemente menos de 1 μM, más preferentemente menos

de 100 nM, y aún más preferentemente menos de 10 nM.

Por ejemplo, la "patología que involucra glucocorticoide" significa

(1) una enfermedad metabólica que incluye diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión o hígado graso,

(2) un síndrome metabólico,

(3) un evento vascular fatal que incluye infarto cardíaco o apoplejía cerebral,

(4) hiperorexia,

(5) una enfermedad neurodisfuncional que incluye disgnosia, enfermedad neurodegenerativa, desórdenes emocionales, esquizofrenia o estímulo del apetito,

(6) una enfermedad asociada con la función de inmunidad disminuida,

(7) glaucoma, o

(8) osteoporosis

y lo similar.

Cuando el compuesto de la presente invención es usado como fármaco para tratamiento o profilaxis de una patología que demuestra que está involucrado el glucocorticoide, puede ser administrado sistémicamente o tópicamente, y oralmente o parenteralmente. Mientras la dosis varía, dependiendo de la edad, el peso del cuerpo, condición, efecto del tratamiento y lo similar, por ejemplo, generalmente puede ser administrada dentro del rango de 0.1 mg a 1 g por administración a un adulto una vez o varias veces por día. El compuesto de la presente invención también puede ser usado como un fármaco para el tratamiento o profilaxis de las enfermedades indicadas precedentemente, sin mencionar al ser

humano, en animales distintos al ser humano, particularmente en los mamíferos. Lo mismo se aplica al uso del compuesto de la presente invención como un fármaco para tratamiento o profilaxis de

(1) una enfermedad metabólica que incluye diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión o hígado graso.

(2) un síndrome metabólico.

(3) un evento vascular fatal que incluye infarto cardíaco o apoplejía cerebral,

(4) hiperorexia,

(5) una enfermedad neurodisfuncional que incluye disgnosia, enfermedad neurodegenerativa, desórdenes emocionales, esquizofrenia o estímulo del apetito,

(6) una enfermedad asociada con la función de inmunidad disminuida.

(7) glaucoma, o

(8) osteoporosis.

y lo similar.

Para producir una preparación del compuesto de la presente invención como una composición sólida o composición líquida para administración oral, o una inyección para administración parental y lo similar, el compuesto puede ser mezclado con aditivos tales como un diluyente conveniente, un agente de dispersión, un adsorbente, un solubilizador y lo similar. Adicionalmene, la composición farmacéutica de la presente invención puede tener una forma conocida tal como tableta, píldora, polvo, gránulo, supositorio, inyección, colirio, líquido, cápsula, pastilla, aerosol, elixir, suspensión, emulsión, jarabe y lo similar.

Cuando la composición farmacéutica de la presente invención, por ejemplo, es una preparación sólida tal como tableta, píldora, polvo, gránulo etc., el aditivo incluye, por ejemplo, lactosa, manitol, glucosa, hidroxipropilcelulosa, celulosa microcristalina, almidón, polivinilpirrolidona, aluminometasilicato de magnesio, polvo de anhídrido silícico y lo similar. Cuando van a ser preparadas una tableta o píldora, se puede aplicar un recubrimiento por película de sustancia gastrosoluble o entérica tal como sacarosa, gelatina, hidroxipropilcelulosa, o ftalato de hidroximetilcelulosa etc. según sea necesario, o se puede producir una tableta de capa múltiple que tiene dos o más capas.

El compuesto, composición farmacéutica, o fármaco de la presente invención puede ser usado en una combinación con (más adelante en la presente también denominado como el uso de una combinación) otra composición farmacéutica o fármaco (más adelante en la presente también denominado un fármaco de combinación).

La planificación de administración de la composición farmacéutica o fármaco de la presente invención, y un fármaco de combinación no está limitada, y las mismas pueden ser administradas al sujeto de administración en la forma de un fármaco de combinación, pueden ser adiminiatradas simultáneamente, o pueden ser adiminiatradas de una manera alternada. Además, puede ser administrado un agente farmacéutico que es característicamente un equipo que contiene la composición farmacéutica o fármaco de la presente invención y un fármaco de combinación. La dosis del fármaco de combinación puede ser una empleada clínicamente la cual puede ser determinada dependiendo apropiadamente del sujeto de administración, edad y peso del cuerpo del sujeto de administración, condición, tiempo de administración, presentación del medicamento, método de administración,

combinación y lo similar. La modalidad de administración del fármaco de combinación no está particularmente limitada, y puede ser cualquiera con la condición que sean combinadas la composición farmacéutica o fármaco de la presente invención, y un fármaco de combinación.

Un agente farmacéutico que comprende de 1 a 3 agentes seleccionados de los siguientes (1) a (5) y el compuesto de la presente invención o una sal del mismo en combinación:

(1) un agente para el tratamiento o profilaxis de hiperlipidemia,

(2) un agente para el tratamiento o profilaxis de obesidad.

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas.

(5) un agente para el tratamiento o profilaxis de hipertensión

significan los agentes farmacéuticos tal como un caso en cual el "agente farmacéutico" es un fármaco de combinación, un caso en el cual el "agente farmacéutico" es un equipo que contiene un fármaco que contiene dichos "1 a 3 agentes seleccionados de (1) a (5)" y un fármaco que contiene el compuesto de la presente invención, un caso en el cual el "agente farmacéutico" y el fármaco que contiene el compuesto de la presente invención son administrados simultáneamente o a ciertos intervalos, y lo similar. Este agente farmacéutico es preferentemente un agente para el tratamiento o profilaxis de una patología que involucra glucocorticoide.

Como el fármaco de combinación, pueden ser indicados

(1) un agente para el tratamiento o profilaxis de hiperlipidemia.

(2) un agente para el tratamiento o profilaxis de obesidad,

(3) un agente para el tratamiento o profilaxis de diabetes,

(4) un agente para el tratamiento o profilaxis de complicaciones diabéticas, y.

(5) un agente para el tratamiento o profilaxis de hipertensión,

y pueden ser usados 1 a 3 de los mismos agentes y el compuesto de la presente invención en combinación.

Como el "agente para el tratamiento o profilaxis de hiperlipidemia", por ejemplo, se puede indicar,

(1) fármacos de fibrato (agonistas del receptor PPAR α),

(2) agonistas de receptor de PPAR-δ,

(3) inhibidores de proteína de transferencia de triglicérido microsomal (MTP).

(4) inhibidores de transferencia de proteína de colesteril éster (CETP),

(5) fármacos de estatina (inhibidores de reductasa HMG-CoA),

(6) resinas de intercambio de anión,

(7) probucol.

(8) fármacos de ácido nicotínico,

(9) fitoesterol,

(10) inductores de apolipoproteína-A1 (Apo-A1),

(11) activadores de lipoproteína lipasa (LPL),

(12) inhibidores de lipasa endotelial,

(13) ezetimibe,

(14) inhibidores de IBAT,

(15) inhibidores de sintasa de escualeno,

(16) inhibidores de ACAT,

(17) agonistas de receptor LXR,

(18) agonistas de receptor FXR,

(19) antagonistas de receptor FXR, y

(20) agonistas de adenosina A1

y específicamente, clofibrato, bezafibrato, fenofibrato, lovastatina, simvastatina, pravastatina, fluvastatina, atorvastatina, pitavastatina, rosuvastatina, cerivastatina, colestiramina, colestimida, nicotinato de tocoferol, nicomol, niceritrol, soisterol, orizanol gamma y lo similar pueden ser indicados.

Como el "agente para el tratamiento o profilaxis de obesidad", por ejemplo, se puede indicar

(1) fármacos leptina.

(2) inhibidores de lipasa pancreáticos,

(3) inhibidores de recaptación de serotonina noradrenalina,

(4) antagonistas de receptor canabinoide,

(5) inhibidores de recaptación de monoamina,

(6) inhibidores de aciltransferasa de diacilglicerol (DGAT),

(7) antagonistas del receptor polipéptido insulinotrópico dependiente de glucosa (GIP).

(8) agonists de receptor de leptin.

(9) agonistas de receptor de bombesina subtipo 3 (BRS-3),

(10) inhibidores de perilipina,

(11) inhibidores de acetil-CoA carboxilasa 1 (ACC1),

(12) inhibidores de acetil-CoA carboxilasa 2 (ACC2).

(13) inhibidores de sintasa de ácido graso,

(14) inhibidores de aciltransferasa de sn-1-acil-glicerol-3-fosfato (AGPAT),

(15) inhibidores de fosfolipasa pancreática A2 (pPLA2),

(16) agonistas del receptor melanocortina (MC),

(17) antagonistas del receptor neuropéptido Y5 (NPY5),

(18) inductores o activadores de proteína de desacoplamiento (UCP),

(19) activadores de carnitina O-palmitoiltransferasa 1 (CPT-1),

(20) agonistas de CCK1 (CCKA),

(21) Factor Neurotrófico ciliar (CNTF),

(22) agonistas de CRF 2,

(23) antagonistas del receptor de neuropéptido Y2 (NPY2),

(24) antagonistas del receptor de neuropéptido Y4 (NPY4),

(25) agonistas beta de receptor hormona tiroidea,

(26) hormonas somatotrópicas,

(27) inhibidores de citrato liasa ATP,

(28) antagonistas de 5-HT6, y

(29) agonistas de 5-HT2C,

y específicamente, se puede indicar leptina, orlistat, sibutramina, rimonabant, y mazindol y lo similar.

Como el "agente para el tratamiento o profilaxis de diabetes", por ejemplo, se puede indicar

(1) preparaciones de insulina (inyección),

(2) preparaciones orales de insulina de bajo peso molecular,

(3) agonistas de receptor de sulfonilurea (agentes SU),

(4) secretagogos de insulina que no son sulfonilurea (agentes SU),

(5) abridores de canal potasio dependiente de ATP (KATP),

(6) inhibidores de glucosidasa,

(7) inhibidores de maltina,

(8) sensibilizador de insulina,

(9) agonistas de receptor tGLP-1 de bajo peso molecular,

(10) análogos de péptido tGLP-1,

(11) inhibidores de dipeptidil peptidasa IV (DPP-IV),

(12) antagonistas de receptor de glucagon,

(13) antagonistas de receptor de glucocorticoide,

(14) biguanidas,

(15) inhibidores de SGLUT.

(16) inhibidores de fructosa-1,6-bisfosfatasa (FBPase),

(17) inhibidores de sintasa de glicógeno quinasa 3 (GSK-3),

(18) inhibidores de fosfoenolpiruvato carboxiquinasa (PEPCK),

(19) inhibidores de la proteína tirosina fosfatasa 1B (PTPase 1B),

(20) inhibidores de fosfatasa inositol que contiene dominio SH2 (SHIP2),

(21) inhibidores de glicógeno fosforilasa (GP),

(22) activadores de glucoquinasa,

(23) agonistas de receptor GPR40,

(24) inhibidores de deshidrogenasa de piruvato de quinasa (PDHK),

(25) inhibidores glutamina: aminotransferasa de fructosa-6-fosfato (GFAT).

(26) antioxidantes; depuradores de óxido nítrico,

(27) inhibidores de carnitina O-palmitoiltransferasa 1 (CPT-1),

(28) factores liberadores de hormona de crecimiento (GHRF).

(29) inhibidores lipasa triacilglicerol (hormona sensible a lipasa),

(30) agonistas de receptor PPAR γ,

(31) antagonistas de receptor PPAR γ,

(32) agonistas de receptor PPAR α/γ,

(33) activadores de proteína quinasa activada por AMP (AMPK),

(34) agonistas de receptor adiponectina, y

(35) agonistas de receptor adrenalina β3,

y específicamente, se puede indicar insulina, tolbutamida, gliclopiramida, acetohexamida, clorpropamida, glibuzol, glibenclamida, gliclazida, glimepirida, mitiglinida, repaglinida, nateglinida, voglibosa, acarbosa, miglitol, maleato de rosiglitazona, clorhidrato de metformina, clorhidrato de pioglitazona, clorhidrato de buformin y lo similar.

Como el "agente para el tratamiento o profilaxis de complicaciones diabéticas", por ejemplo, se puede indicar

(1) inhibidor de proteína quinasa C β (PKCβ),

(2) antagonista del receptor de angiotensina II,

(3) inhibidor de reductasa aldosa,

(4) inhibidor de la enzima que convierte angiotensina (AS),

(5) inhibidores de la producción de los productos finales de glicación avanzados (AGE),

(6) agentes terapéuticos para neuropatía, y

(7) agentes terapéuticos para nefropatía diabética,

y específicamente, epalrestat (kinedak), clorhidrato de mexiletina, clorhidrato de imidapril y lo similar.

Como el "agente para el tratamiento o profilaxis de hipertensión", por ejemplo, se puede indicar

(1) diuréticos de tiazida,

(2) diuréticos similares a tiazida,

(3) diuréticos de lazo,

(4) diuréticos de mantenimiento de K,

(5) bloqueadores de β,

(6) bloqueadores de α,β,

(7) bloqueadores de α,

(8) neurosupresores de simpático central,

(9) neurosupresores de simpático periférico (preparaciones rauwolfia).

(10) antagonista de Ca (benzotiazepina),

(11) antagonistas de Ca (dihidropiridina),

(12) vasodilatadores,

(13) inhibidores de la enzima angiotensina que convierte angiotensina (AS),

(14) antagonistas del receptor angiotensina II,

(15) fármaco de nitrato,

(16) antagonistas de receptor endotelina ETA,

(17) inhibidores de enzima convertidora de endotelina; inhibidores de Neprilisina,

(18) prostaglandina; agonistas de prostanoide FP.

(19) inhibidores de renina,

(20) mejoradores de expresión NOS3; análogos de prostaciclina.

(21) inhibidores de fosfodiesterasa V (PDE5A),

(22) análogos de prostaciclina, y

(23) antagonistas de aldosterona,

y específicamente, se puede indicar hidroclorotiazida, triclormetiazida, bencilhidroclorotiazida, meticrano, indapamida, tripamida, clortalidona, mefrusida, furosemida, espironolactona, triamtereno, atenolol, fumarato de bisoprolol, clorhidrato de betaxolol, clorhidrato de bevantolol, tartrato de metoprolol, clorhidrato de acebutolol, clorhidrato de celiprolol, nipradilol, clorhidrato de tilisolol, Nadolol, clorhidrato de propranolol, clorhidrato de indenolol, clorhidrato de carteolol, pindolol, preparación de pindolol de liberación prolongada, clorhidrato de bunitrolol, sulfato de penbutolol, malonato de bopindolol, clorhidrato de amosulalol, clorhidrato de arotinolol, carvedilol, clorhidrato de labetalol, urapidil, clorhidrato de terazosina, mesilato de doxazosina, clorhidrato de bunazosina, clorhidrato de prazosina, mesilato de fentolamina, clorhidrato de clonidina, clorhidrato de guanfacina, acetato de guanabenz, metildopa, reserpina, rescinamina, besilato de amlodipina, aranidipina, clorhidrato de efonidipina, cilnidipina, clorhidrato de nicardipina, nisoldipina, nitrendipina, nifedipina, preparación de nifedipina de liberación prolongada, nilvadipina, clorhidrato de barnidipina, felodipina, clorhidrato de benidipina, clorhidrato de manidipina, azelnidipina, clorhidrato de diltiazem, clorhidrato de hidrazina, clorhidrato de todoralazina, budralazina, cadralazina, captopril, maleato de enalapril, alacepril, clorhidrato de delapril, cilazapril, lisinopril, clorhidrato de benazepril, clorhidrato de imidapril, clorhidrato de temocapril, clorhidrato de quinapril, trandolapril, erbumina de perindopril, candesartancilexetil, valsartan, termisartan, medoxomil olmesartan, nitroprusida de sodio, nitroglicerina y lo similar.

Como el fármaco de combinación, se puede indicar un fármaco que eleva el nivel de glucocorticoide de la sangre, como el corticosteroide suprarrenal y lo similar. El glucocorticoide de la sangre no sólo significa glucocorticoides endógenos, tal como corticoesterona, cortisol y lo similar, sino también glucocorticoides exógenos

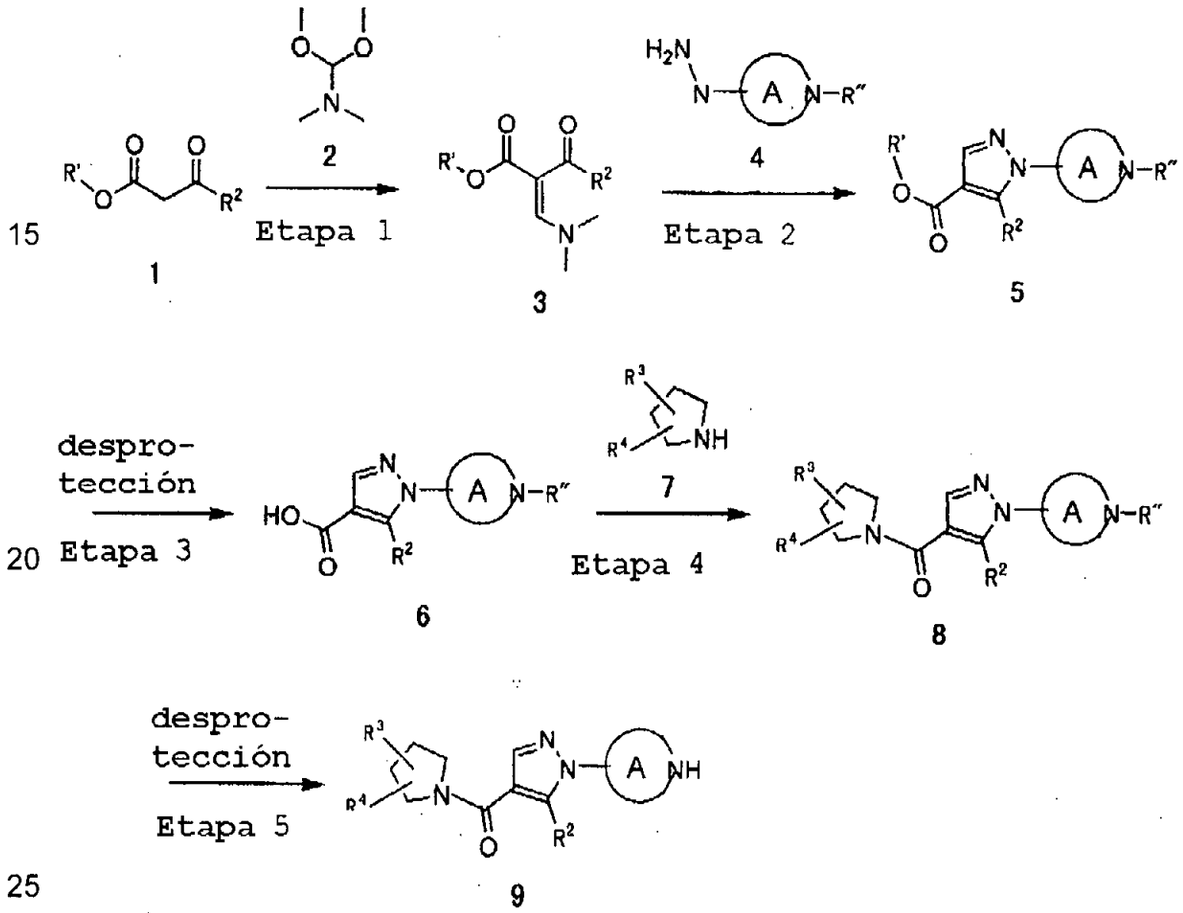
debido a la administración de corticoesteroide suprarrenal. Se pueden usar uno a tres agentes de los mismos y el compuesto de la presente invención en combinación.

Se ilustran algunos ejemplos de los métodos de producción de los compuestos de la presente invención más adelante. Sin embargo, los métodos de producción de los compuestos de la presente invención no se limitan a estos ejemplos. Aún en ausencia de descripción del método de producción, la producción eficaz se puede realizar, cuando sea necesario, introduciendo un grupo protector en un grupo funcional seguido por la desprotección en una etapa subsiguiente, intercambiando el orden de etapas respectivas. Como el grupo protector, por ejemplo, un grupo protector de carboxilo (en la presente, el grupo protector de carboxilo generalmente significa aquéllos usados en el campo de la química orgánica sintética, tal como grupo metilo, grupo etilo, grupo propilo, grupo ter-butilo, grupo bencilo, grupo p-metoxibencilo y lo similar, el cual está en forma de ésteres capaces de ser fácilmente transformados al ácido carboxílico por hidrólisis, hidrogenación catalítica y lo similar), un grupo protector de amino (en la presente, grupo protector de amino generalmente significa aquéllos usados en el campo de química de síntesis orgánica, tal como grupo ter-butoxicarbonilo, grupo benciloxicarbonilo, grupo bencilo y lo similar los cuales puede ser fácilmente transformados a un grupo amino por hidrólisis, hidrogenación catalítica y lo similar), un grupo protector de grupo hidroxilo (en la presente, el grupo protector de grupo hidroxilo generalmente significa aquéllos usados en el campo de química de síntesis orgánica, tal como grupo tetrahidropiranilo, grupo metoximetilo, grupo metoxietoximetilo, grupo benciloximetilo, grupo bencilo, grupo p-metoxibencilo, grupo p-nitrobencilo, grupo trimetilsililo, grupo t-butildimetilsililo, grupo acetilo, grupo benzoilo, grupo alilo, grupo t-butilo y lo similar que pueden ser fácilmente transformados a un grupo hidroxilo por hidrólisis,

hidrogenación catalítica y lo similar), y lo similar puede ser indicado. La preparación después de la reacción en cada etapa se puede aplicar por un método típico, en donde el aislamiento y purificación es realizada seleccionando o combinando métodos convencionales según sea necesario, tal como cristalización, recristalización, cromatografía de gel de sílice, HPLC preparativa y lo similar.

Método de producción 1

En el compuesto [1'] de la presente invención, un compuesto en donde -X- es -NH- se puede producir por las etapas siguientes.



en donde R' es un grupo protector de carboxilo (en la presente, el grupo protector de carboxilo generalmente significa aquéllos usados en el campo de química de síntesis orgánica, tal como grupo metilo, grupo etilo, grupo propilo, grupo ter-butilo, grupo bencilo, grupo p-metoxibencilo y lo similar) el cual está en la forma de ésteres capaces de ser transformados fácilmente al ácido carboxílico por hidrólisis, hidrogenación catalítica y lo similar, R" es un grupo protector de amino (en la presente, el grupo protector de amino generalmente significa aquéllos usados en el campo de química de síntesis orgánica, como el tert-butoxicarbonilo grupo, benciloxicarbonilo grupo, grupo bencilo y lo similar) el cual puede ser fácilmente eliminado por hidrólisis, hidrogenación catalítica y lo similar, y los otros símbolos son iguales a los definidos precedentemente.

Etapa 1

El compuesto (3) se puede obtener haciendo reaccionar β-cetoéster (1) sintetizado por un método conocido con dimetilacetal dimetilformamida (2) en un solvente o en ausencia de un solvente. Como el solvente, se puede indicar metanol, etanol, benceno, tolueno, xileno, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 20°C a 250°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de dimetilacetal dimetilformamida (2) a ser usada es generalmente de aproximadamente 1.5 - aproximadamente 3 mol, por 1 mol de β-cetoéster (1). La cantidad del solvente a ser usado no está limitada particularmente y puede ser determinada dependiendo apropiadamente del tipo y cantidad de uso del sustrato de la reacción (β-cetoéster (1) y dimetilacetal dimetilformamida (2)), temperatura de reacción, tiempo de reacción y lo similar (lo mismo se aplica a la cantidad del solvente a ser usado en cada etapa a ser explicada más adelante).

Etapa 2: Etapa para la construcción del anillo de pirazol.

El compuesto (5) se obtiene haciendo reaccionar hidrazina (4) sintetizada por un método conocido con el compuesto (3) en un solvente. Como el solvente, se puede indicar metanol, etanol, n-propanol, n-butanol, isopropanol, acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 20°C a 250°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de hidrazina (4) a ser usada es generalmente de aproximadamente 1 - aproximadamente 2 mol, por 1 mol de compuesto (3). Cuando la hidrazina (4) es una sal, la reacción se realiza en presencia de una base (la cantidad de base a ser usada es generalmente de aproximadamente 1 - aproximadamente 2 mol, por 1 mol de compuesto (3)), tal como carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, acetato de sodio, acetato de potasio, hidróxido de sodio, hidróxido de potasio, hidróxido de litio, trietilamina, N,N-diisopropiletilamina, piridina y lo similar.

Etapa 3: Etapa de desprotección de grupo protector de carboxilo.

El compuesto (6) se obtiene eliminando el grupo protector de carboxilo R' del compuesto (5) por un método conocido.

Etapa 4: Etapa de amidación

El compuesto (8) se obtiene haciendo reaccionar el compuesto (6) con amina (7) en un solvente en presencia de un agente de condensación y un aditivo. Como el agente de condensación, se puede indicar diciclohexilcarbodiimida (DCC), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (WSC×HCl), diisopropilcarbodiimida, 1,1'-carbonildiimidazol (CDI), difenilfosforil azida (DPPA) y lo similar. Como aditivo, se puede indicar 1-hidroxibenzotriazol (HOBT), imida N-

hidroxisuccínica (HOSu), 4-dimetilaminopiridina (DMAP) y lo similar. Como solvente, se puede indicar diclorometano, cloroformo, acetonitrilo, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 20°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de amina (7) ser usado es generalmente aproximadamente 1 - aproximadamente 1.5 mol por 1 mol de compuesto (6). Adicionalmene, la cantidad del agente de condensación y el aditivo a ser usado es generalmente de aproximadamente 1 - aproximadamente 1.5 mol y aproximadamente 1 - aproximadamente 1.5 mol, respectivamente, por 1 mol de compuesto (6). Cuando la amina (7) es una sal, la reacción es realizada en presencia de una base tal como carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, acetato de sodio, acetato de potasio, hidróxido de sodio, hidróxido de potasio, hidróxido de litio, trietilamina, N,N-diisopropiletilamina, piridina y lo similar. Alternativamente, el ácido carboxílico (6) se puede conducir a un haluro ácido o un anhídrido de mezcla de ácidos y se puede hacer reaccionar con amina (7) en presencia de una base. La cantidad de base a ser usada es generalmente de aproximadamente 1 - aproximadamente 1.5 mol por 1 mol de compuesto (6).

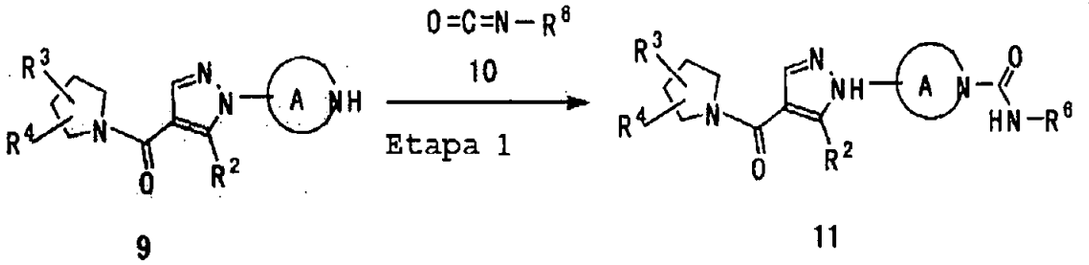
Etapa 5: Etapa de desprotección de grupo protector de amino

El compuesto (9) se obtiene eliminando el grupo protector de amino R" del compuesto (8) por un método conocido. Cuando sea necesario, se puede convertir a una sal por un método conocido.

Método de producción 2.

En el compuesto [1'] de la presente invención, un compuesto en donde

-X- es -N(R^1)- y R^1 es -CONR^{5}R^6 en donde R^5 es un átomo de hidrógeno se puede producir por las etapas siguientes.



9 11

en donde cada símbolo es igual al definido anteriormente.

Etapa 1: Etapa de ureación

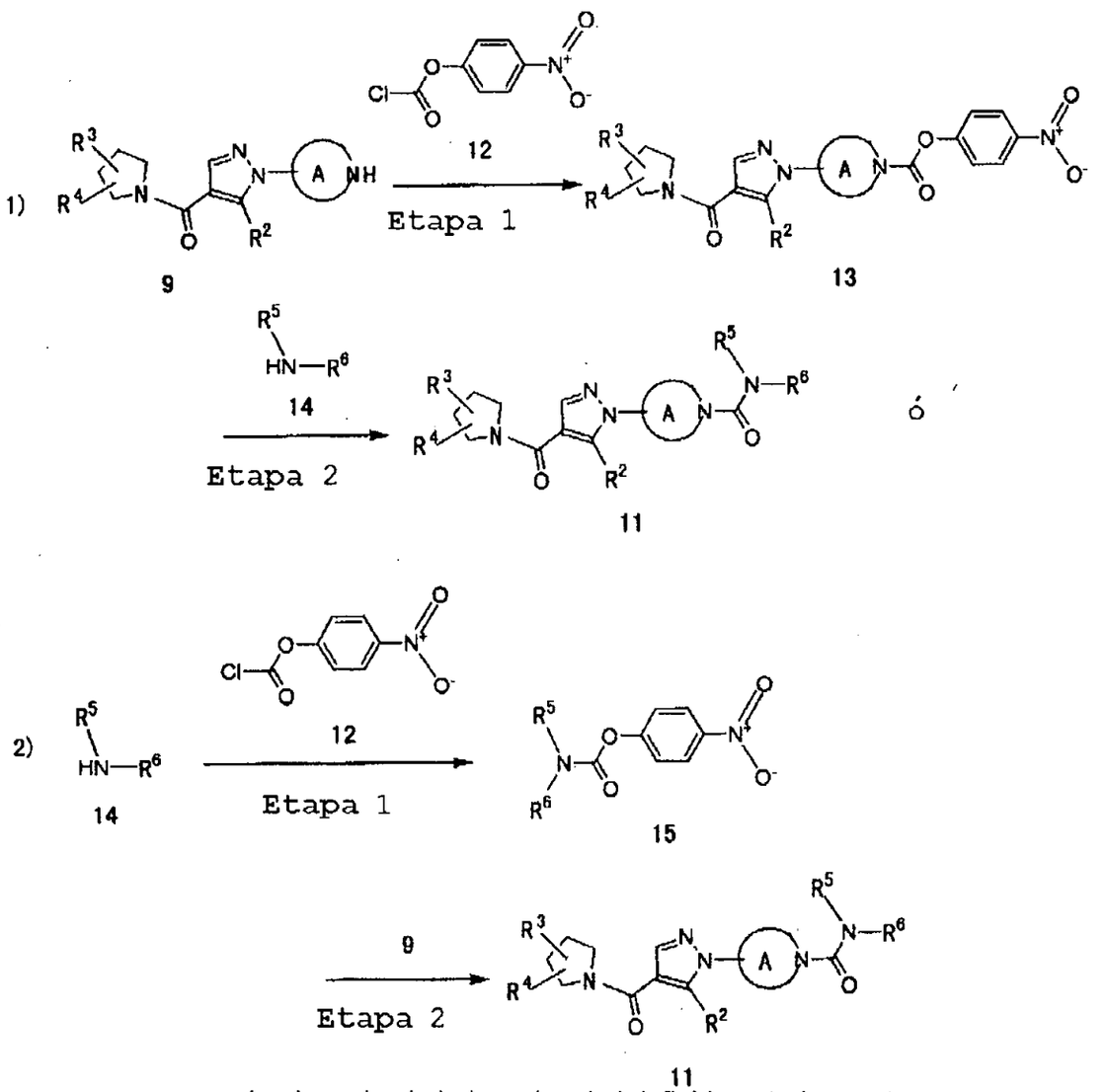
1) cuando R^6 es distinto del hidrógeno.

El compuesto (11) se obtiene haciendo reaccionar el compuesto (9) con isocianato (10) en un solvente. Como el solvente, se puede indicar acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, dimetilsulfóxido, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 0°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de isocianato (10) a ser usado es generalmente de aproximadamente 1 - aproximadamente 2 mol por 1 mol de compuesto (9). Cuando la amina (9) es una sal, la reacción se lleva a cabo en presencia de una base tal como trietilamina, N,N-diisopropiletilamina, la piridina y lo similar (la cantidad de la base a ser usada es generalmente de aproximadamente 1 - aproximadamente 2 mol por 1 mol de compuesto (9)). Alternativamente, el compuesto (9) se puede hacer reaccionar con 1,1'-carbonildiimidazol (CDI) (La cantidad de CDI a ser usado es generalmente de aproximadamente 1 - aproximadamente 3 mol por 1 mol de compuesto (9)), y entonces se hace reaccionar con la amina correspondiente.

Cuando R^6 es un grupo alquilo, grupo cicloalquilo, grupo arilo, grupo heterocíclico etc. que posee un grupo funcional, el mismo puede ser protegido apropiadamente con un grupo protector y, después de la ureación, es desprotegido. Cuando el grupo alquilo, grupo cicloalquilo, grupo arilo, grupo heterocíclico y lo similar tienen sustituyentes, los mismos se pueden convertir, después de ureación, a otros grupos funcionales por métodos conocidos. Por ejemplo, se puede indicar la conversión del grupo hidroxilo al grupo alcoxilo o cetona, del grupo amino al alquilamino grupo, grupo alquilcarbonilamino o grupo alquilsulfonilamino, del grupo alcoxicarbonilo al grupo carboxilo, grupo aminocarbonilo, grupo alquilaminocarbonilo o grupo hidroximetilo, y del sulfuro a la sulfona o sulfóxido.

2) cuando R^6 es hidrógeno.

El compuesto (11) se obtiene haciendo reaccionar el compuesto (9) con el cianato en un solvente. Como el solvente, se puede indicar acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, agua, ácido acético, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 0°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de cianato a ser usado es generalmente de aproximadamente 1 - aproximadamente 10 mol, por 1 mol de compuesto (9). Cuando la amina (9) es una sal, la reacción es realizada en presencia de una base como el carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, acetato de sodio, acetato de potasio, hidróxido de sodio, hidróxido de potasio, hidróxido de litio, trietilamina, N,N-diisopropiletilamina, piridina y lo similar (la cantidad de la base a ser usada es generalmente de aproximadamente 1 - aproximadamente 2 mol, por 1 mol de compuesto (9)).



en donde cada símbolo es igual al definido anteriormente.

Etapa 1: Etapa de fenilcarbamación.

El compuesto (13) se obtiene haciendo reaccionar el compuesto (9) con cloroformato de 4-nitrofenilo (12) en un solvente en presencia de una base. Como el solvente, se puede indicar acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, dimetilsulfóxido, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. Como la base, se puede indicar trietilamina, N,N-diisopropiletilamina, piridina y lo similar. La

temperatura de reacción generalmente es de 0°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de cloroformato de 4-nitrofenilo (12) a ser usado es generalmente de aproximadamente 1 - aproximadamente 2 mol por 1 mol de compuesto (9). La cantidad de la base a ser usada es generalmente de aproximadamente 1 - aproximadamente 2 mol, por 1 mol de compuesto (9). Cuando la amina (9) es una sal, la reacción es realizada con una base en una cantidad de aproximadamente 2 - aproximadamente 4 mol por 1 mol de compuesto (9).

Etapa 2: Etapa de ureación.

El compuesto (11) se obtiene haciendo reaccionar el compuesto intermedio de fenilcarbamato (13) con la amina (14) en un solvente. Como el solvente, se puede indicar acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, N-metilpirrolidona, dimetilsulfóxido, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 0°C a 150°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de amina (14) a ser usada es generalmente de aproximadamente 1 - aproximadamente 3 mol por 1 mol de compuesto (9). Cuando la amina (14) es una sal, la reacción es realizada en presencia de una base tal como trietilamina, N,N-diisopropiletilamina, piridina y lo similar (la cantidad de la base a ser usada es generalmente de aproximadamente 1 - aproximadamente 3 mol por 1 mol de compuesto (13)).

Como un método diferente, según lo ilustrado en la fórmula 2), el compuesto (15) se obtiene en la etapa 1 haciendo reaccionar la amina (14) con cloroformato de 4-nitrofenilo (12) en un solvente, y el compuesto (15) se hace reaccionar con la amina (9) en la etapa 2 para dar el compuesto (11).

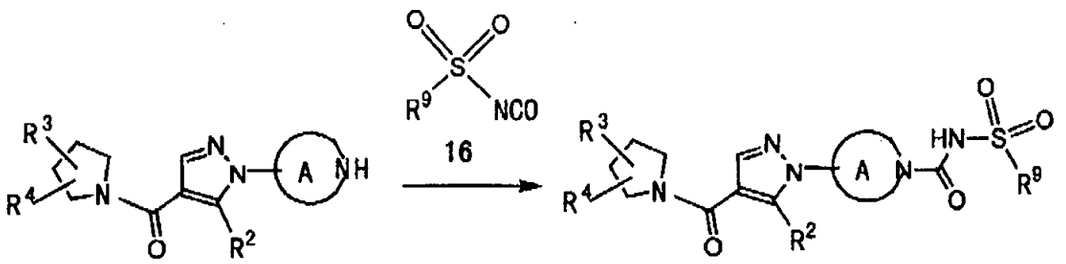
Además, se puede usar otros cloroformatos o 1,1'-carbonildiimidazol

(CDI) en lugar de cloroformato de 4-nitrofenilo (12).

Cuando R^5 y/o R^6 son/es grupo alquilo, grupo cicloalquilo, grupo arilo, grupo heterocíclico etc. que poseen un grupo funcional, los mismos son apropiadamente protegidos con un grupo protector y, después de ureación, son desprotegidos. Cuando el grupo alquilo, grupo cicloalquilo, grupo arilo, grupo heterocíclico y lo similar tienen sustituyente(s), los mismos se pueden convertir a otros grupos funcionales después de ureación por un método conocido. Por ejemplo, se puede indicar la conversión del grupo hidroxilo al grupo alcoxilo o cetona, del grupo amino al grupo alquilamino, grupo alquilcarbonilamino o grupo alquilsulfonilamino, grupo alcoxicarbonilo al grupo carboxilo, grupo aminocarbonilo, grupo alquilaminocarbonilo o grupo hidroximetilo, y del sulfuro a la sulfona o sulfóxido.

Método de producción 4.

En el compuesto [1'] de la presente invención, un compuesto en donde -X- es $-N(R^1)-$, R^1 es $-CONR^5R^6$ en donde R^5 es un átomo de hidrógeno, y R^6=$-S(=O)_2R^9$) puede ser producido por las etapas siguientes.



en donde cada símbolo es igual al definido anteriormente.

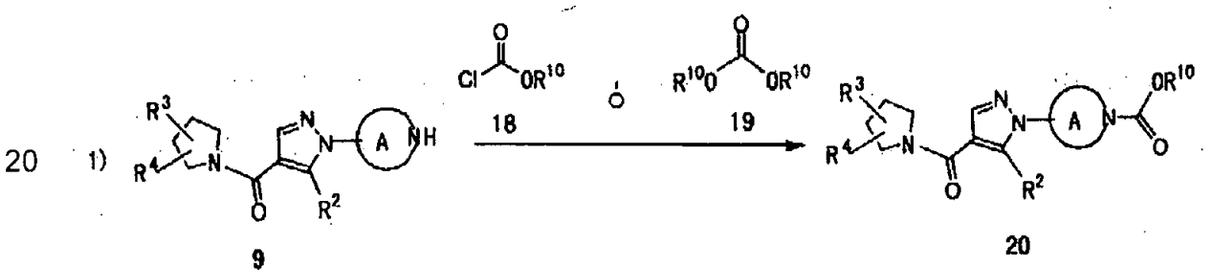
Etapa 1: Etapa de sulfonilureación

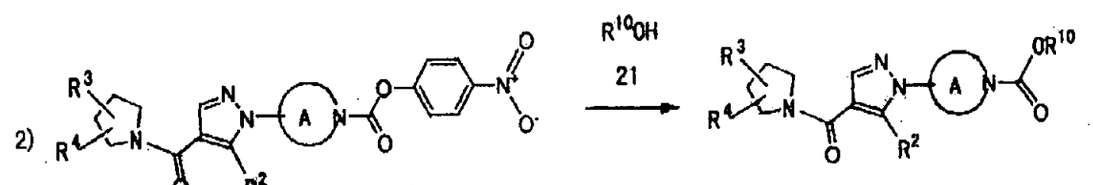
El compuesto (17) se obtiene haciendo reaccionar el compuesto (9)

con sulfonilisocianato (16) en un solvente. Como el solvente, se puede indicar acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, dimetilsulfóxido, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 0°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de sulfonilisocianato (16) a ser usada es generalmente de aproximadamente 1 - aproximadamente 2 mol por 1 mol de compuesto (9). Cuando la amina (9) es una sal, la reacción es realizada en presencia de una base tal como trietilamina, N,N-diisopropiletilamina, piridina y lo similar (la cantidad de la base a ser usada es generalmente de aproximadamente 1 - aproximadamente 2 mol por 1 mol de compuesto (9)).

Método de producción 5.

En el compuesto [1'] de la presente invención, un compuesto en donde -X- es -N(R^1)- y R^1 es -COOR^{10} se puede producir por las etapas siguientes.





en donde cada símbolo es igual al definido anteriormente.

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Etapa 1: Etapa de carbamación

El compuesto (20) se obtiene haciendo reaccionar el compuesto (9) con clorocarbonato (18) o carbonato (19) en presencia de una base, en un solvente o sin solvente. Como el solvente, se puede indicar acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, dimetilsulfóxido, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. Como la base, se puede indicar trietilamina, N,N-diisopropiletilamina, piridina y lo similar. La temperatura de reacción generalmente es de 0°C a 150°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de clorocarbonato (18) o carbonato (19) a ser usada es generalmente de aproximadamente 1 - aproximadamente 2 mol por 1 mol de compuesto (9). La cantidad de la base a ser usada es generalmente de aproximadamente 1 - aproximadamente 2 mol por 1 mol de compuesto (9). Cuando la amina (9) es una sal, la reacción es realizada con una base en una cantidad de aproximadamente 2 - aproximadamente 4 mol por 1 mol de compuesto (9).

Cuando R^{10} es grupo alquilo, grupo cicloalquilo, grupo arilo, grupo heterocíclico etc. que posee un grupo funcional, los mismos son apropiadamente protegidos con un grupo protector y, después de la carbamación, son desprotegidos. Cuando el grupo alquilo, grupo cicloalquilo, grupo arilo, grupo heterocíclico y lo similar tienen sustituyente(s), los mismos pueden ser convertidos a otros grupos funcionales después de la carbamación por un método conocido. Por ejemplo, se puede indicar la conversión del grupo hidroxilo al grupo alcoxilo o cetona, del grupo amino al grupo alquilamino, grupo alquilcarbonilamino o grupo alquilsulfonilamino, del grupo alcoxicarbonilo al grupo carboxilo, grupo aminocarbonilo, grupo alquilaminocarbonilo o grupo hidroximetilo, y del sulfuro a la sulfona o sulfóxido.

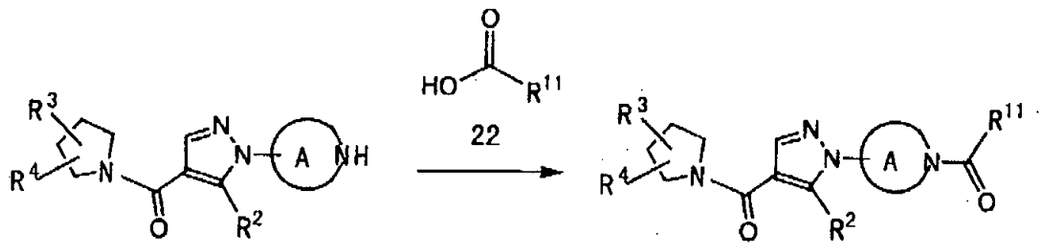
Como un método diferente, según lo ilustrado en la fórmula 2), el compuesto intermedio de fenilcarbamato (13) obtenido en el Método de Producción 3, etapa 1 se hace reaccionar con el alcohol (21) en un solvente, en presencia de una base para dar el Compuesto (20). Como el solvente, se puede indicar acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, N-metilpirrolidona, dimetilsulfóxido, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. Como la base, el hidruro de sodio, hidruro de potasio, carbonato de sodio, carbonato de potasio, hidróxido de sodio, hidróxido de potasio, hidróxido de litio, trietilamina, N,N-diisopropiletilamina, piridina y lo similar. La temperatura de reacción generalmente es de 0°C a 150°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de alcohol (21) a ser usada es generalmente de aproximadamente 1 - aproximadamente 3 mol por 1 mol de intermedio del fenilcarbamato (13). La cantidad de la base a ser usada es generalmente de aproximadamente 1 - aproximadamente 2 mol por 1 mol de intermedio del fenilcarbamato (13).

Cuando R^{10} es grupo alquilo, cicloalquilo grupo, grupo arilo, grupo heterocíclico, etc. que posee un grupo funcional, los mismos son apropiadamente protegidos con un grupo protector y, después de la carbamación, son desprotegidos. Cuando el grupo alquilo, grupo cicloalquilo, grupo arilo, grupo heterocíclico y lo similar tienen sustituyente(s), los mismos pueden ser convertidos a otros grupos funcionales después de la carbamación por un método conocido. Por ejemplo, se puede indicar la conversión del grupo hidroxilo al grupo alcoxilo o cetona, del grupo amino al grupo alquilamino, grupo alquilcarbonilamino o grupo alquilsulfonilamino, del grupo alcoxicarbonilo al grupo carboxilo, grupo aminocarbonilo, grupo alquilaminocarbonilo o grupo hidroximetilo, y del sulfuro a la sulfona o sulfóxido.

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Método de producción 6.

En el compuesto [1'] de la presente invención, un compuesto en donde -X- es -N(R^1)-, y R^1 es -COR^{11} se puede producir por las etapas siguientes.



en donde cada símbolo es igual al definido anteriormente.

Etapa 1: Etapa de amidación

El compuesto (23) se obtiene haciendo reaccionar el compuesto (9) con ácido carboxílico (22) en un solvente en presencia de un agente de condensación y un aditivo. Como el agente de condensación, se puede indicar diciclohexilcarbodiimida (DCC), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (WSC×HCl), diisopropilcarbodiimida, 1,1'-carbonildiimidazol (CDI), difenilfosforil azida (DPPA) y lo similar. Como aditivo, se puede indicar 1-hidroxibenzotriazol (HOBT), imida N-hidroxisuccínica (HOSu), 4-dimetilaminopiridina (DMAP) y lo similar. Como solvente, se puede indicar diclorometano, cloroformo, acetonitrilo, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 20°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de ácido carboxílico (22) a ser usado es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol por 1 mol de compuesto (9). Adicionalmene, la cantidad del agente de condensación y el aditivo a ser usado es

generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol, respectivamente, por 1 mol de compuesto (9). Cuando el compuesto (9) es una sal, la reacción es realizada en presencia de una base tal como carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, acetato de sodio, acetato de potasio, hidróxido de sodio, hidróxido de potasio, hidróxido de litio, trietilamina, N,N-diisopropiletilamina, piridina y lo similar. Además, el ácido carboxílico (22) se puede conducir a un haluro ácido o un anhídrido de mezcla de ácidos y se puede hacer reaccionar con el compuesto (9) en presencia de una base. La cantidad de la base a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol por 1 mol de compuesto (9).

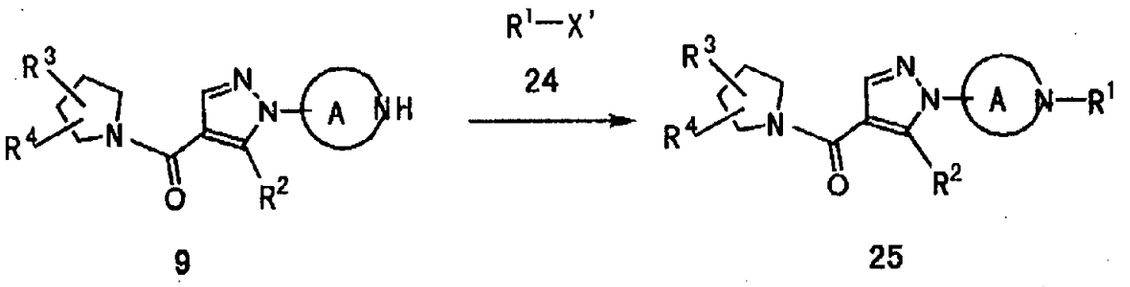
Cuando R^{11} es grupo alquilo, grupo cicloalquilo, grupo arilo, grupo heterocíclico, etc. que posee un grupo funcional, los mismos son apropiadamente protegidos con un grupo protector y, después de la amidación, son desprotegidos. Cuando el grupo alquilo, grupo cicloalquilo, grupo arilo, grupo heterocíclico y lo similar posee sustituyente(s), los mismos pueden se pueden convertir a otros grupos funcionales después de la amidación por un método conocido.

Por ejemplo, se puede mencionar la conversión del grupo hidroxilo al grupo alcoxilo o cetona, del grupo amino al grupo alquilamino, grupo alquilcarbonilamino o grupo alquilsulfonilamino, grupo alcoxicarbonilo al grupo carboxilo, grupo aminocarbonilo, grupo alquilaminocarbonilo o grupo hidroximetilo, y del sulfuro a sulfona o sulfóxido.

Método de producción 7

En el compuesto [1'] de la presente invención, un compuesto en donde -X- es $-N(R^1)-$ y R^1 es grupo alquilo de C_{1-6} o grupo cicloalquilo que puede ser

producido mediante las etapas siguientes.



en donde X' es un átomo de halógeno y los otros símbolos son iguales a los definidos precedentemente.

Etapa 1: Etapa de N-alquilación.

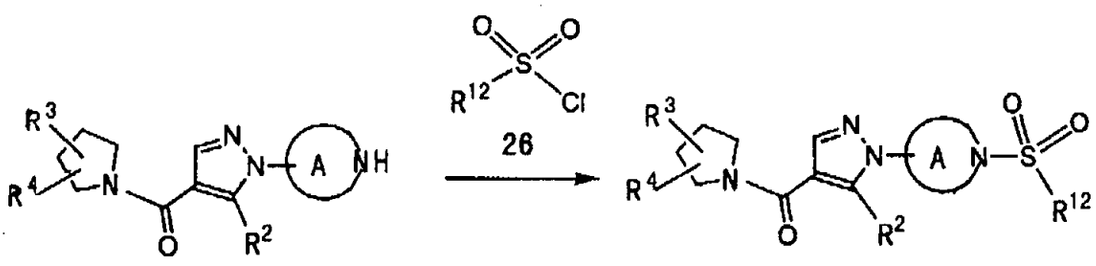
El compuesto (25) se obtiene haciendo reaccionar el compuesto (9) con alquilhaluro (24) en un solvente en presencia de una base. Como la base, se puede indicar carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, acetato de sodio, acetato de potasio, hidróxido de sodio, hidróxido de potasio, hidróxido de litio, hidruro de sodio, hidruro de potasio, trietilamina, N,N-diisopropiletilamina, piridina y lo similar. Como el solvente, se puede indicar acetonitrilo, acetona, éter dietilico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, dimetilsulfóxido, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 0°C a 100°C. El tiempo de reacción generalmente es de 30 min a 24 h. La cantidad de alquilhaluro (24) a ser usado es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de compuesto (9). La cantidad de la base a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de compuesto (9). Cuando la amina (9) es una sal, la reacción es realizada con una base en una cantidad de aproximadamente 2 hasta aproximadamente 4 mol por 1 mol de compuesto (9). También es posible

realizar aminación reductiva del compuesto (9) con el aldehído correspondiente, cetona, o un equivalente del mismo.

Cuando R^1 es un grupo alquilo que tiene un grupo funcional, es apropiadamente protegido con un grupo protector y, después de la N-alquilación, es desprotegido. Cuando el grupo alquilo tiene sustituyente(s), puede ser convertido en otro grupo funcional después de N-alquilación por un método conocido. Por ejemplo, se puede indicar la conversión del grupo hidroxilo al grupo alcoxilo o cetona, del grupo amino al grupo alquilamino, grupo alquilcarbonilamino o grupo alquilsulfonilamino, grupo alcoxicarbonilo al grupo carboxilo, grupo aminocarbonilo, grupo alquilaminocarbonilo o grupo hidroximetilo, y desde el sulfuro a la sulfona o sulfóxido.

Método de producción 8.

En el compuesto [1'] de la presente invención, un compuesto en donde -X- es $-N(R^1)-$ y R^1 es $-S(=O)_2R^{12}$ se puede producir mediante las etapas siguientes.



en donde cada símbolo es igual al definido anteriormente.

Etapa 1: Etapa de sulfonilación

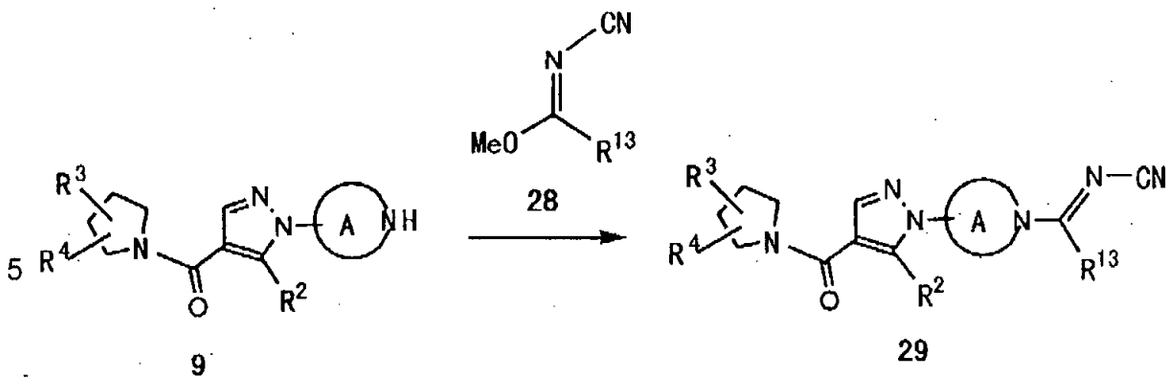
El compuesto (27) se puede obtener haciendo reaccionar el compuesto (9) con cloruro de sulfonilo (26) en un solvente en presencia de una base. Como la base, se puede indicar carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, acetato de sodio, acetato de potasio,

hidróxido de sodio, hidróxido de potasio, hidróxido de litio, hidruro de sodio, hidruro de potasio, trietilamina, N,N-diisopropiletilamina, piridina y lo similar. Como el solvente, se puede indicar acetonitrilo, acetona, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, dimetilsulfóxido, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 0°C a 100°C. El tiempo de reacción generalmente es de 30 min a 24 h. La cantidad de cloruro de sulfonilo (26) a ser usado es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de compuesto (9). La cantidad de la base a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de compuesto (9). Cuando la amina (9) es una sal, la reacción es realizada con una base en una cantidad de aproximadamente 2 hasta aproximadamente 4 mol por 1 mol de compuesto (9). Adicionalmene, el compuesto (9) se puede hacer reaccionar con el anhídrido sulfónico correspondiente.

Cuando R^{12} es un grupo alquilo que posee un grupo funcional, es apropiadamente protegido con un grupo protector y, después de la sulfonilación, son desprotegidos. Cuando el grupo alquilo tiene sustituyente(s), puede ser convertido en otro grupo funcional después de la sulfonilación por un método conocido. Por ejemplo, se puede indicar la conversión del grupo hidroxilo al grupo alcoxilo o cetona, del grupo amino al alquilamino grupo, grupo alquilcarbonilamino o grupo alquilsulfonilamino, del grupo alcoxicarbonilo al grupo carboxilo, grupo aminocarbonilo, grupo alquilaminocarbonilo o grupo hidroximetilo, y del sulfuro a la sulfona o sulfóxido.

Método de producción 9.

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en donde cada símbolo es igual al definido anteriormente.

Etapa 1: Etapa de la producción de N-cianoamidina

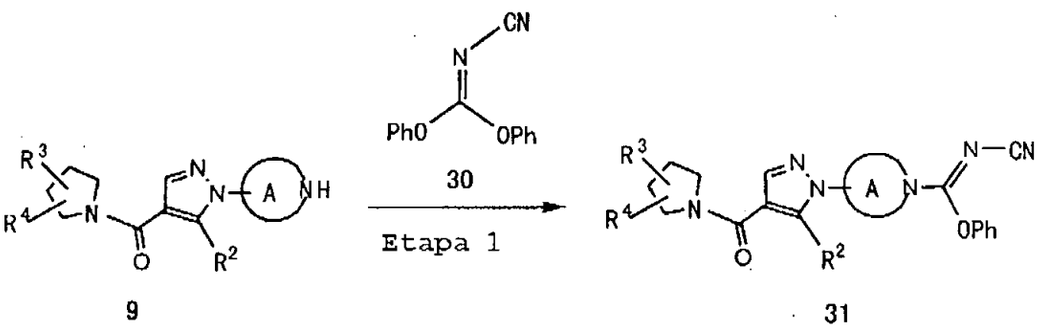
El compuesto (29) se obtiene haciendo reaccionar el compuesto (9) con N-cianoimidoacetato (28) en un solvente. Como el solvente, se puede indicar acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, dimetilsulfóxido, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 0°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de N-cianoimidoacetato (28) a ser usado es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de compuesto (9). Cuando la amina (9) es una sal, la reacción es realizada en presencia de una base tal como trietilamina, N,N-diisopropiletilamina, piridina y lo similar (la cantidad de la base a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de compuesto (9)).

Método de producción 10.

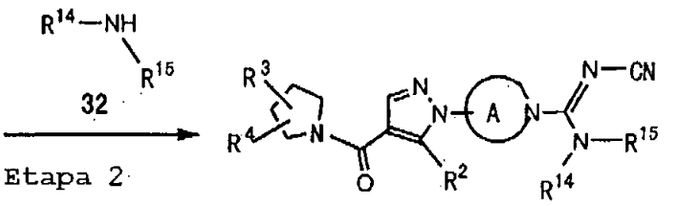
En el compuesto [1'] de la presente invención, un compuesto en donde -X- está representado por -N(R^1)- y R^1 es -C(=NCN)N$R^{14}R^{15}$ se puede producir por

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las etapas siguientes.



9 31



33

en donde el Ph es un grupo fenilo y los otros símbolos son iguales a los definidos precedentemente.

Etapa 1

El compuesto (31) se obtiene haciendo reaccionar el compuesto (9) con difenil N-cianocarbonimidato (30) en un solvente. Como el solvente, se puede indicar acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, dimetilsulfóxido, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 0°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de difenil N-cianocarbonimidato (30) a ser usado es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de compuesto (9). Cuando la amina (9) es una sal, la reacción es realizada en presencia de una base tal como trietilamina, N,N-diisopropiletilamina, piridina y lo similar (la cantidad de la base a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de

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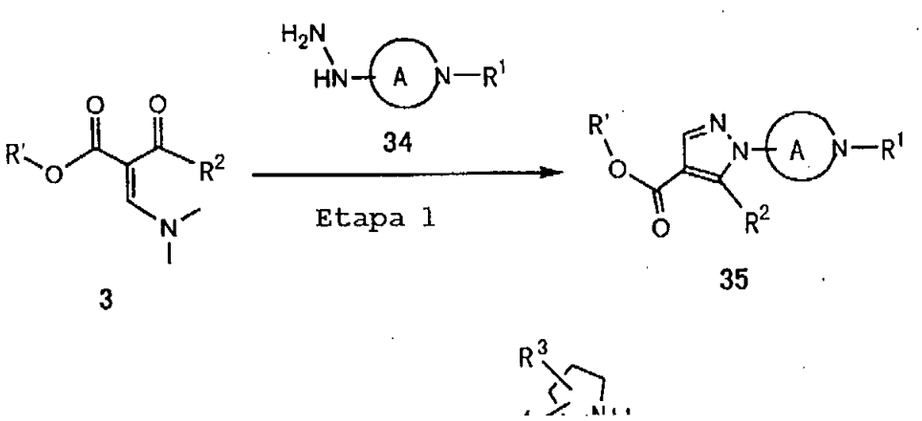
compuesto (9)).

Etapa 2: Etapa de producción de N-cianoguanidina.

El compuesto (33) se obtiene haciendo reaccionar el compuesto (31) con la amina (32) en un solvente. Como el solvente, se puede indicar acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, N-metilpirrolidona, dimetilsulfóxido, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 0°C a 150°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de amina (32) a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 5 mol por 1 mol de compuesto (31). Cuando la amina (32) es una sal, la reacción es realizada en presencia de una base tal como trietilamina, N,N-diisopropiletilamina, piridina y lo similar (la cantidad de la base a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 20 mol por 1 mol de compuesto (31)).

Método de producción 11.

En el compuesto [1'] de la presente invención, un compuesto en donde -X- es -N(R^1)- y R^1 es un grupo arilo o grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros puede ser producido por las etapas siguientes.



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en donde cada símbolo es igual al definido anteriormente.

Etapa 1: Etapa para la construcción del anillo de pirazol desde hidrazina (34) y compuesto (3)

El compuesto (35) se obtiene haciendo reaccionar hidrazina (34) sintetizada por un método conocido con el compuesto (3) obtenido en el Método de producción 1, etapa 1, en un solvente. Como el solvente, se puede indicar metanol, etanol, n-propanol, n-butanol, isopropanol, acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 20°C a 250°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de hidrazina (34) a ser usada es generalmente de aproximadamente 1.5 hasta aproximadamente 3 mol por 1 mol de compuesto (3). Cuando la hidrazina (34) es una sal, la reacción es realizada en presencia de una base tal como carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, acetato de sodio, acetato de potasio, hidróxido de sodio, hidróxido de potasio, hidróxido de litio, trietilamina, N,N-diisopropiletilamina, piridina y lo similar (la cantidad de la base a ser usada es generalmente de aproximadamente 1.5 hasta aproximadamente 3 mol por 1 mol de compuesto (3)).

Etapa 2: Etapa de desprotección de grupo protector de carboxilo R'

El compuesto (36) se obtiene eliminando el grupo protector de

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carboxilo R' por un método conocido.

Etapa 3: Etapa de amidación.

El compuesto (37) se obtiene haciendo reaccionar el compuesto (36) con la amina (7) en un solvente en presencia de un agente de condensación y un aditivo. Como el agente de condensación, se puede indicar diciclohexilcarbodiimida (DCC), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (WSC×HCl), diisopropilcarbodiimida, 1,1'-carbonildiimidazol (CDI), difenilfosforil azida (DPPA) y lo similar. Como el aditivo, se puede indicar 1-hidroxibenzotriazol (HOBT), imida N-hidroxisuccínica (HOSu), 4-dimetilaminopiridina y lo similar. Como el solvente, se puede indicar diclorometano, cloroformo, acetonitrilo, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es 20°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de amina (7) a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol por 1 mol de compuesto (36). Adicionalmene, la cantidad del agente de condensación y el aditivo a ser usado es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol y aproximadamente 1 hasta aproximadamente 1.5 mol, respectivamente, por 1 mol de compuesto (36). Cuando la amina (7) es una sal, la reacción es realizada en presencia de una base tal como carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, acetato de sodio, acetato de potasio, hidróxido de sodio, hidróxido de potasio, hidróxido de litio, trietilamina, N,N-diisopropiletilamina, piridina y lo similar. Adicionalmene, el ácido carboxílico (36) puede ser transformado a un haluro ácido y entonces se puede hacer reaccionar con la amina (7) en presencia de una base. La cantidad de la base a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol por 1 mol de

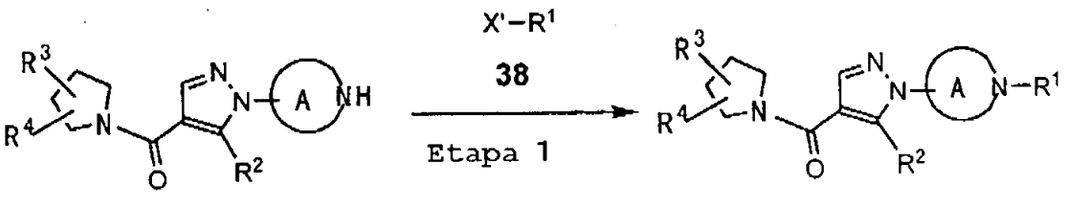
463

compuesto (36).

Cuando R^1 es grupo arilo o un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros que posee un grupo funcional, es apropiadamente protegido con un grupo protector y después de esto es desprotegido. Cuando el grupo arilo o grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros tienen sustituyente(s), puede ser convertido en otro grupo funcional por un método conocido después de esta etapa. Por ejemplo, la conversión del grupo hidroxilo al grupo alcoxilo o cetona, del grupo amino al grupo alquilamino, grupo alquilcarbonilamino o grupo alquilsulfonilamino, del grupo alcoxicarbonilo al grupo carboxilo, grupo aminocarbonilo, grupo alquilaminocarbonilo o grupo hidroximetilo, y del sulfuro a la sulfona o sulfóxido.

Método de producción 12.

En el compuesto [1'] de la presente invención, un compuesto en donde -X- es $-N(R^1)-$ y R^1 es un grupo arilo o grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros puede ser producidi por las etapas siguientes.



9 **39**

en donde cada símbolo es igual al definido anteriormente.

Etapa 1: Etapa de aminación tipo Buchwald/Hartwig catalizada por paladio

El compuesto (39) se obtiene haciendo reaccionar el compuesto (9)

obtenido en el Método de producción 1 y haluro aromático (38) en un solvente en presencia de un catalizador de paladio y una base. Como catalizador de paladio, se puede indicar una mezcla de acetato de paladio y 2,2'-bis(difenilfosfino)-1,1'-binaftilo, bicloruro de bis(difenilfosfino)ferroceno paladio (II), tris(dibencilidenacetona) dipaladio y lo similar. Como la base, se puede indicar fosfato de tripotasio (K_3PO_4), carbonato de sodio, carbonato de potasio, carbonato de cesio, carbonato ácido de sodio, carbonato ácido de potasio, ter-butóxido de potasio y lo similar. Como el solvente, se puede indicar 1,2-dimetoxietano, tetrahidrofurano, 1,4-dioxano, benceno, tolueno, xileno, ter-butanol, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 20°C a 250°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de haluro aromático (38) a ser usado es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol por 1 mol de compuesto (9). La cantidad del catalizador de paladio y la base a ser usada es generalmente de aproximadamente 0.01 hasta aproximadamente 0.1 mol y aproximadamente 1 hasta aproximadamente 2 mol, respectivamente, por 1 mol de compuesto (9).

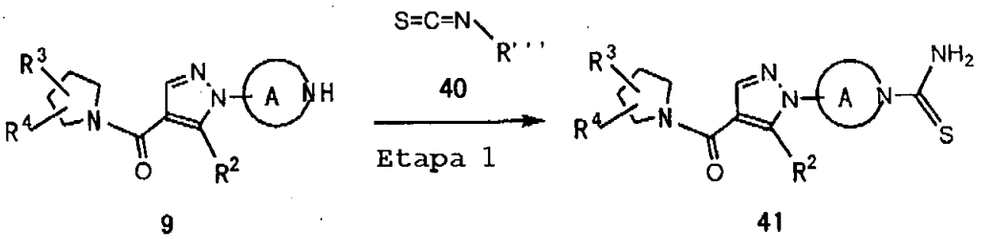
Cuando R^1 es un grupo arilo o un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros que posee un grupo funcional, es apropiadamente protegido con un grupo protector y después de esto es desprotegido. Cuando el grupo arilo o un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros tiene sustituyente(s), puede ser convertido en otro grupo funcional después de esta etapa por un método conocido.

Por ejemplo, se puede indicar la conversión del grupo hidroxilo al grupo alcoxilo o cetona, del grupo amino al grupo alquilamino, grupo alquilcarbonilamino o grupo alquilsulfonilamino, grupo alcoxicarbonilo al grupo carboxilo, grupo aminocarbonilo, grupo alquilaminocarbonilo o grupo hidroximetilo, y

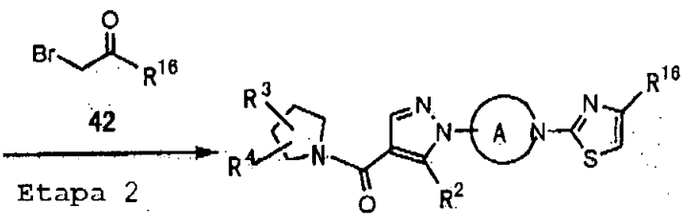
sulfuro a sulfona o sulfóxido.

Método de producción 13.

En el compuesto [1'] de la presente invención, un compuesto en donde -X- es -N(R^1)- y R^1 es un grupo arilo o grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros se puede producir por las etapas siguientes.



9 41



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en donde R''' es un sustituyente (por ejemplo, grupo etoxicarbonilo, grupo benzoilo, grupo 9-fluorenilmetoxicarbonilo y lo similar) en el átomo de nitrógeno, y los otros símbolos son iguales a los definidos precedentemente.

Etapa 1: Etapa de tioureación

El compuesto (41) se obtiene haciendo reaccionar el compuesto (9) obtenido en el Método de producción 1 con isotiocianato (40) en un solvente y eliminando el sustituyente (R''') en el átomo de nitrógeno por un método conocido. Como el isotiocianato (40), se puede indicar etoxicarbonilisotiocianato, benzoilisotiocianato, 9-fluorenilmetoxicarbonil-isotiocianato y lo similar. Como el solvente, se puede indicar acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano,

N,N-dimetilformamida, dimetilsulfóxido, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 0°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de isotiocianato (40) a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de compuesto (9). Es posible hacer reaccionar el compuesto (9) con tiofosgeno (la cantidad de tiofosgeno a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol por 1 mol de compuesto (9)), seguido por un tratamiento de amonio.

Etapa 2: Etapa para construcción del anillo de tiazol.

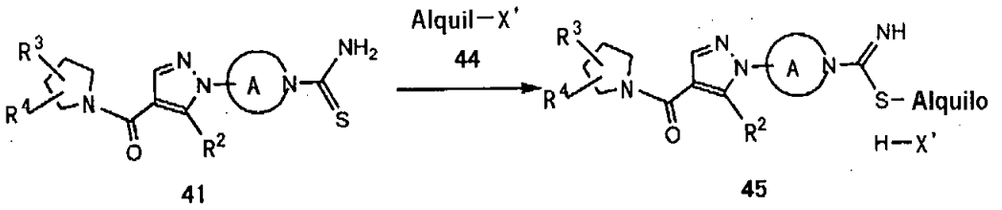
El compuesto (43) se obtiene haciendo reaccionar el compuesto (41) con halometilcetona (42) en un solvente. Como el solvente, se puede indicar metanol, etanol, n-propanol, n-butanol, isopropanol, acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 20°C a 250°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de halometilcetona (42) a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol por 1 mol de compuesto (41).

Un grupo tiazolilo que tiene un grupo funcional puede ser protegido apropiadamente con un grupo protector y después de esto es deprotegido. Cuando el grupo tiazolilo tiene sustituyente(s), puede ser convertido en otro grupo funcional después de esta etapa por un método conocido. Por ejemplo, la conversión del grupo hidroxilo al grupo alcoxilo o cetona, del grupo amino a grupo alquilamino, grupo alquilcarbonilamino o grupo alquilsulfonilamino, del grupo alcoxicarbonilo al grupo carboxilo, grupo aminocarbonilo, grupo alquilaminocarbonilo o grupo hidroximetilo, y

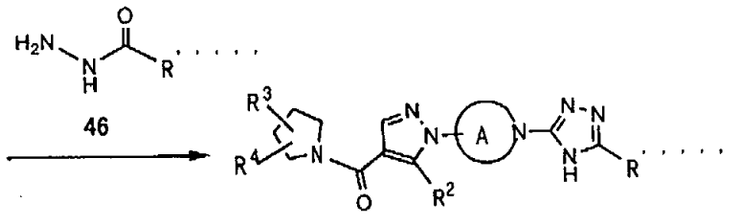
del sulfuro a la sulfona o sulfóxido.

Método de producción 14.

En el compuesto [1'] de la presente invención, un compuesto en donde -X- es -N(R^1)- y R^1 es un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros puede ser producido por las etapas siguientes.



41 45



46 47

en donde X' es un átomo de halógeno, Alquilo es un grupo alquilo de C_{1-6}, R'''' es un grupo carboxilo, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del átomo halógeno y grupo hidroxilo), o un grupo cicloalquilo y los otros símbolos son iguales a los definidos precedentemente.

Etapa 1

El hidrohaluro de isotiourea (45) se obtiene haciendo reaccionar el compuesto (41) obtenido en el Método de producción 13, etapa 1 con alquilhaluro (44) en un solvente. Como el solvente, se puede indicar acetonitrilo, acetona, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, dimetilsulfóxido, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 0°C a 100°C. El tiempo de reacción generalmente es de 30 min a 24 h. La cantidad de alquilhaluro (44) a ser usado es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de compuesto (41).

Etapa 2: Etapa para la construcción del anillo de triazol desde isotiourea e hidrazida.

El compuesto (47) se puede obtener haciendo reaccionar hidrohaluro de isotiourea (45) con hidrazida (46) sintetizada por un método conocido en un solvente en presencia de una base. Como solvente, se puede indicar metanol, etanol, n-propanol, isopropanol, n-butanol, acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, dimetilsulfóxido, diclorometano, 1,2-dicloroetano, cloroformo, benceno, clorobenceno, O-diclorobenceno, tolueno, xileno, piridina, 2,6-lutidina, 2,4,6-colidina, ácido acético, agua, y un solvente mezcla de los mismos y lo similar. Como la base, se puede indicar hidróxido de sodio, hidróxido de potasio, hidróxido de litio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, acetato de sodio, acetato de potasio, hidruro de sodio, hidruro de potasio, trietilamina, N,N-diisopropiletilamina, piridina y lo similar. La temperatura de reacción generalmente es de 20°C a 250°C. El tiempo de reacción generalmente es de 30 min a 24 h. La cantidad de hidrazida (46) a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de hidrohaluro de isotiourea (45). La cantidad de base a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de hidrohaluro de isotiourea (45). Cuando la hidrazida (46) es una sal, la reacción es realizada con una base en una cantidad de aproximadamente 2 hasta aproximadamente 4 mol por 1 mol de hidrohaluro de isotiourea (45).

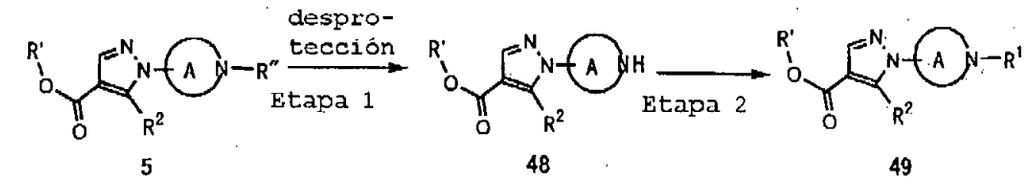
Un grupo triazolilo que posee un grupo funcional que puede ser protegido apropiadamente con un grupo protector y después de esto es desprotegido. Cuando el grupo triazolilo tiene sustituyente(s), el sustituyente(s) puede ser convertido por un método conocido a otro grupo funcional después de esta etapa. Por ejemplo, se puede indicar la conversión del grupo hidroxilo al grupo alcoxilo o cetona, del grupo amino al grupo alquilamino, grupo alquilcarbonilamino o grupo

470

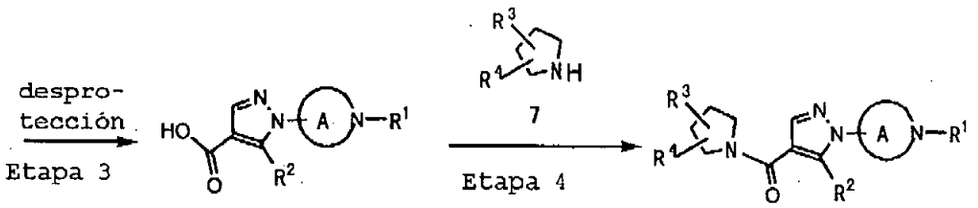
alquilsulfonilamino, grupo alcoxicarbonilo al grupo carboxilo, grupo aminocarbonilo, grupo alquilaminocarbonilo o grupo hidroximetilo, y del sulfuro a sulfona o sulfóxido.

Método de producción 15

En el compuesto [1'] de la presente invención, un compuesto en donde -X- es -N(R^1)- se puede producir por las etapas siguientes.



5 48 49



50 51

en donde cada símbolo es igual al definido anteriormente.

Etapa 1: Etapa de desprotección de grupo protector de amino.

El compuesto (48) se obtiene eliminando el grupo protector de amino R" del compuesto (5) obtenido en el Método de producción 1, etapa 2.

Etapa 2: Introducción de R^1

El compuesto (49) se obtiene introduciendo R^1 en el compuesto (48) por un método similar a los Métodos de Producción 2 a 10, y Métodos de Producción 12 a 14.

Etapa 3: Etapa de desprotección de grupo protector de carboxilo

El compuesto (50) se obtiene eliminando el grupo protector de carboxilo R' del compuesto (49) por un método conocido.

471

Etapa 4: Etapa de amidación.

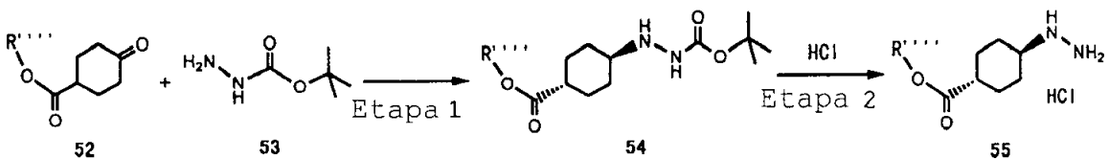
El compuesto (51) se obtiene haciendo reaccionar el compuesto (50) con la amina (7) en un solvente en presencia de un agente de condensación y un aditivo. Como el agente de condensación, se puede indicar diciclohexilcarbodiimida (DCC), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (WSC×HCl), diisopropilcarbodiimida, 1,1'-carbonildiimidazol (CDI), difenilfosforil azida (DPPA) y lo similar. Como aditivo, se puede indicar 1-hidroxibenzotriazol (HOBT), imida N-hidroxisuccínica (HOSu), 4-dimetilaminopiridina (DMAP) y lo similar. Como solvente, se puede indicar diclorometano, cloroformo, tetrahidrofurano, acetonitrilo, 1,4-dioxano, N,N-dimetilformamida, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 20°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de amina (7) a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol por 1 mol de compuesto (50). Adicionalmene, la cantidad del agente de condensación y el aditivo a ser usado es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol y aproximadamente de 1 hasta aproximadamente 1.5 mol, respectivamente, por 1 mol de compuesto (50). Cuando la amina (7) es una sal, la reacción es realizada en presencia de una base tal como carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, acetato de sodio, acetato de potasio, hidróxido de sodio, hidróxido de potasio, hidróxido de litio, trietilamina, N,N-diisopropiletilamina, piridina y lo similar (la cantidad de la base a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol por 1 mol de compuesto (50)).

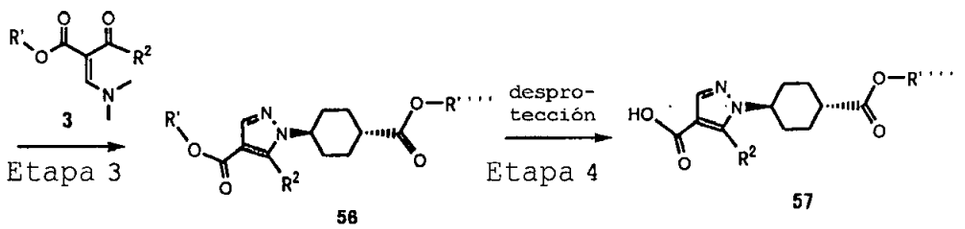
El R^1 que tiene un grupo funcional es apropiadamente protegido con un grupo protector y después de esto es desprotegido. Cuando R^1 tiene

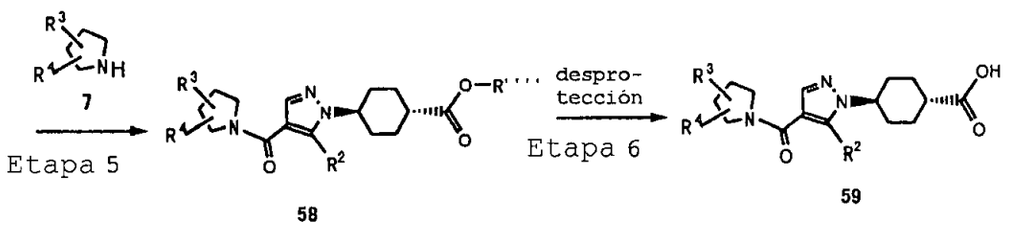
sustituyente(s), puede ser convertido en otro grupo funcional después de esta etapa por un método conocido. Por ejemplo, se puede indicar la conversión del grupo hidroxilo al grupo alcoxilo o cetona, del grupo amino al grupo alquilamino, grupo alquilcarbonilamino o grupo alquilsulfonilamino, del grupo alcoxicarbonilo al grupo carboxilo, grupo aminocarbonilo, grupo alquilaminocarbonilo o grupo hidroximetilo, y del sulfuro a la sulfona o sulfóxido.

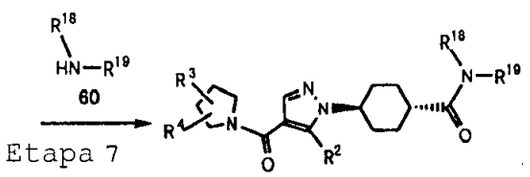
Método de producción 16

En el compuesto [1'] de la presente invención, un compuesto en donde -X- es -C(R^7R^8)- se puede producir por las etapas siguientes.









en donde cada símbolo es igual al definido anteriormente donde R''''

es un grupo protector de carboxilo (en la presente, el grupo protector de carboxilo generalmente significa aquéllos usados en el campo de química de síntesis orgánica, tal como grupo metilo, grupo etilo, grupo propilo, grupo ter-butilo, grupo bencilo, grupo p-metoxibencilo y lo similar, el cual está en la forma de ésteres capaces de ser transformados fácilmente al ácido carboxílico por hidrólisis, hidrogenación catalítica y lo similar).

Etapa 1: Alquilación reductiva

El compuesto (54) se obtiene haciendo reaccionar la cetona (52) con carbazato de ter-butilo (53) en un solvente en presencia de un agente reductor. Como el agente reductor, se puede indicar borohidruro de sodio, cianoborohidruro de sodio, triacetoxiborohidruro de sodio, complejo borano y lo similar. Como el solvente, se puede indicar metanol, etanol, n-propanol, n-butanol, isopropanol, diclorometano, cloroformo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, benceno, tolueno, xileno, ácido acético, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 0°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad del agente reductor ser usado es generalmente de aproximadamente 2 hasta aproximadamente 5 mol, por 1 mol de compuesto (52).

Etapa 2: des-BOC (grupo ter-butoxicarbonilo).

El compuesto (54) se hace reaccionar con solución de ácido clorhídrico 4N en acetato de etilo, o solución de ácido clorhidrico 4N en 1,4-dioxano para dar el clorhidrato de hidrazina (55). Adicionalmene, después del des-BOC por la acción del ácido trifluoracético en un solvente, puede ser convertido al clorhidrato. Como solvente, se puede indicar diclorometano, cloroformo y lo similar.

Etapa 3: Etapa para la construcción del anillo de pirazol desde clorhidrato de hidrazina (55) y compuesto (3)

El compuesto (56) se obtiene haciendo reaccionar el clorhidrato de hidrazina (55) con el compuesto (3) en un solvente en presencia de una base. Como solvente, se puede indicar metanol, etanol, n-propanol, n-butanol, isopropanol, acetonitrilo, éter dietílico, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, diclorometano, cloroformo, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. Como la base, se puede indicar carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, acetato de sodio, acetato de potasio, hidróxido de sodio, hidróxido de potasio, hidróxido de litio, trietilamina, N,N-diisopropiletilamina, piridina y lo similar. La temperatura de reacción generalmente es de 20°C a 250°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de clorhidrato de hidrazina (55) a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de compuesto (3). La cantidad de la base a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de compuesto (3).

Etapa 4: Etapa de desprotección de grupo protector de carboxilo

El compuesto (57) se obtiene eliminando el grupo protector de carboxilo R' del compuesto (56) por un método conocido.

Etapa 5: Etapa de amidación.

El compuesto (58) se obtiene haciendo reaccionar el compuesto (57) con la amina (7) en un solvente en presencia de agente de condensación y un aditivo. Como el agente de condensación, se puede indicar diciclohexilcarbodiimida (DCC), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (WSC×HCl),

diisopropilcarbodiimida, 1,1'-carbonildiimidazol (CDI), difenilfosforil azida (DPPA) y lo similar. Como el aditivo, se puede indicar 1-hidroxibenzotriazol (HOBT), imida N-hidroxisuccínica (HOSu), 4-dimetilaminopiridina (DMAP) y lo similar. Como solvente, se puede indicar diclorometano, cloroformo, acetonitrilo, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 20°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de amina (7) a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol por 1 mol de compuesto (57). Adicionalmene, la cantidad del agente de condensación y el aditivo a ser usado es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol y aproximadamente 1 hasta aproximadamente 1.5 mol, respectivamente, por 1 mol de compuesto (57). Cuando la amina (7) es una sal, la reacción es realizada en presencia de una base tal como carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, acetato de sodio, acetato de potasio, hidróxido de sodio, hidróxido de potasio, hidróxido de litio, trietilamina, N,N-diisopropiletilamina, piridina y lo similar. Adicionalmene, ácido carboxílico (57) puede ser transformado a un haluro ácido o un anhídrido de ácido mixto y se puede hacer reaccionar con la amina (7) en presencia de una base. La cantidad de la base a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol por 1 mol de compuesto (57).

Etapa 6: Etapa de desprotección de grupo protector de carboxilo

El ácido carboxílico (59) se obtiene eliminando el grupo protector de carboxilo R'''' del compuesto (58) por un método conocido.

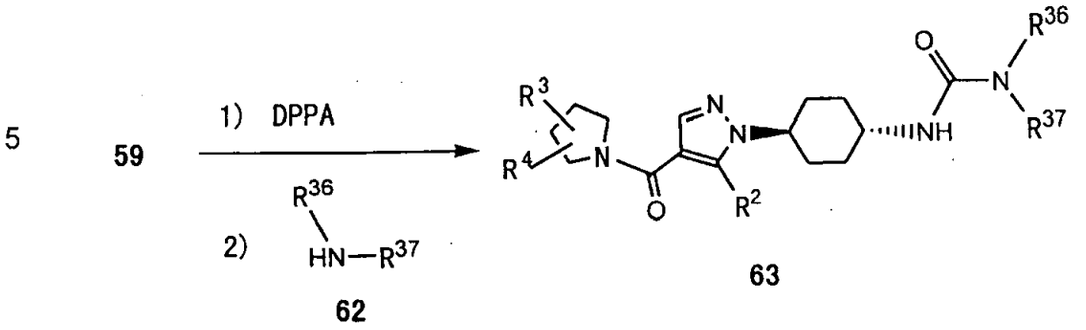
Etapa 7: Etapa de amidación.

El compuesto (61) se obtiene haciendo reaccionar el ácido carboxílico

(59) con la amina (60) en un solvente en presencia de agente de condensación y un aditivo. Como agente de condensación, se puede indicar diciclohexilcarbodiimida (DCC), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (WSC×HCl), diisopropilcarbodiimida, 1,1'-carbonildiimidazol (CDI) o, difenilfosforil azida (DPPA) y lo similar. Como aditivo, se puede indicar 1-hidroxibenzotriazol (HOBT), imida N-hidroxisuccínica (HOSu), 4-dimetilaminopiridina (DMAP) y lo similar. Como solvente, se puede indicar diclorometano, cloroformo, acetonitrilo, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 20°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad de amina (60) a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol por 1 mol de ácido carboxílico (59). Adicionalmene, la cantidad del agente de condensación y el aditivo a ser usado es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol y aproximadamente 1 hasta aproximadamente 1.5 mol, respectivamente, por 1 mol de compuesto (59). Cuando la amina (60) es una sal, la reacción es realizada en presencia de una base tal como carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato hidrógeno de potasio, acetato de sodio, acetato de potasio, hidróxido de sodio, hidróxido de potasio, hidróxido de litio, trietilamina, N,N-diisopropiletilamina, piridina y lo similar. Además, el ácido carboxílico (59) puede ser transformado a un haluro ácido o un anhídrido de ácido mixto y se puede hacer reaccionar con amina (60) en presencia de una base. La cantidad de la base a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 1.5 mol por 1 mol de ácido carboxílico (59).

Método de producción 17

En el compuesto [1'] de la presente invención, un compuesto en donde -X- es -C(R^7R^8)- se puede producir por las etapas siguientes.

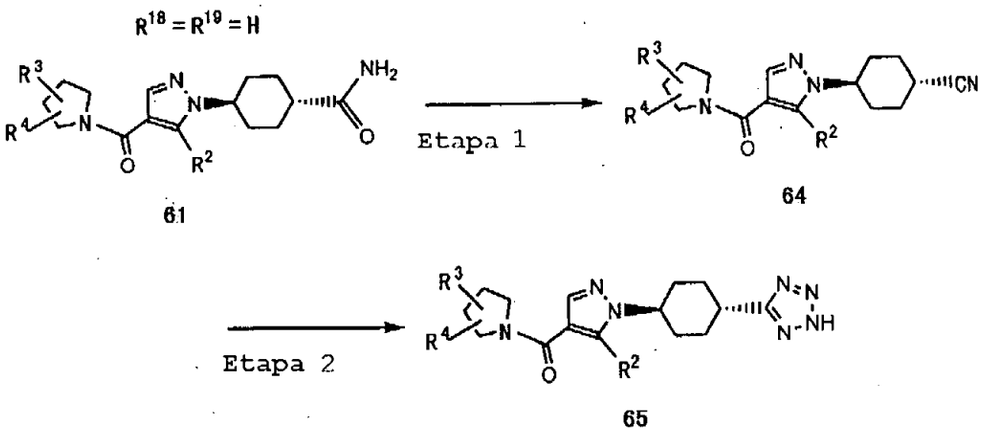


Etapa 1

en donde cada símbolo es igual al definido anteriormente.

Etapa 1: Etapa de ureación.

El ácido carboxílico (59) se hace reaccionar con difenilfosforil azida (DPPA) en un solvente en presencia de una base para obtener un isocianato que se hace reaccionar con la amina (62) para dar la urea (63). Como solvente, se puede indicar diclorometano, cloroformo, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, benceno, tolueno, xileno y lo similar. Como la base, se puede indicar trietilamina, N,N-diisopropiletilamina, piridina y lo similar. La temperatura de reacción para la etapa de producir isocianato generalmente es de 20°C a 150°C, y la etapa para dar urea generalmente es de 0°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h para ambas etapas. La cantidad de DPPA a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de ácido carboxílico (59). La cantidad de la base a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de ácido carboxílico (59). La cantidad de amina (62) a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 5 mol por 1 mol de ácido carboxílico (59).



en donde cada símbolo es igual al definido anteriormente.

Etapa 1: Etapa de cianación.

Se obtiene el nitrilo (64) haciendo reaccionar la amida (61) con un agente de deshidratación en un solvente en presencia de una base. Como el agente de deshidratación, se puede indicar anhídrido de ácido trifluorometansulfónico, cloruro de p-toluensulfonilo, cloruro de tricloroacetilo, anhídrido de ácido trifluoracético, oxicloruro de fósforo, cloruro de tionilo y lo similar. Como la base, se puede indicar trietilamina, N,N-diisopropiletilamina, piridina y lo similar. Como solvente, se puede indicar diclorometano, cloroformo, tetrahidrofurano, 1,4-dioxano, N,N-dimetilformamida, piridina, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 20°C a 100°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad del agente de deshidratación a ser usado es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de amida (61). La cantidad de la base a ser usada es generalmente de aproximadamente 1 hasta aproximadamente 2 mol, por 1 mol de amida (61).

Etapa 2: Etapa para la construcción del anillo de tetrazol

Se hace reaccionar el nitrilo (64) en un solvente en presencia de un reactivo de azidación para dar tetrazol (65). Como el reactivo de azidación, se puede

480

indicar azida de sodo, azidotrimetilestaño, azidotributilestaño, azidotrimetilsilano y lo similar. Como solvente, se puede indicar diclorometano, cloroformo, tetrahidrofurano, 1,2-dimetoxietano, 1,4-dioxano, N,N-dimetilformamida, benceno, tolueno, xileno, y un solvente mezcla de los mismos y lo similar. La temperatura de reacción generalmente es de 20°C a 150°C. El tiempo de reacción generalmente es de 1 h a 24 h. La cantidad del reactivo de azidación a ser usado es generalmente de aproximadamente 1 hasta aproximadamente 2 mol por 1 mol de nitrilo (64).

Los métodos de la producción descritos en esta descripción son ejemplos de los métodos de producción del compuesto de la presente invención, y los compuestos distintos de aquéllos explicados anteriormente pueden ser producidos combinando los métodos convencionales conocidos en el campo de la química de síntesis orgánica.

EJEMPLOS

Los compuestos heterocíclicos y métodos de producción de los mismos de la presente invención se explican en detalle a continuación con referencia a los Ejemplos, los cuales no deberán ser interpretados como limitativos de la misma.

Ejemplo 1

Producción de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-3-(piridin-3-il)pirrolidina

Etapa 1

Producción de 2-ciclopropilcarbonil-3-dimetilaminoacrilato de metilo

3-Ciclopropil-3-oxopropionato de metilo (2.0 g) fue disuelto en tolueno

(20 ml). Fue agregada dimetilformamida de dimetilacetilo (3.0 ml) a la solución obtenida y la mezcla fue calentada a reflujo por 3 h. La mezcla de reacción fue enfriada y fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:acetona=2:1) para producir el compuesto del título como un aceite amarillo (2.61 g).

Etapa 2

Producción de 1-(1-benciloxicarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carboxilato de metilo

Fue sintetizado 2-ciclopropilcarbonil-3-dimetilaminoacrilato de metilo (1.0 g) producido en la etapa anterior, y clorhidrato de 4-hidrazinopiperidin-1-carboxilato de bencilo (1.49 g) sintetizado por un método conocido, fueron suspendidos en etanol. A la suspensión obtenida le fue agregada trietilamina (0.78 ml) y la mezcla fue calentada a reflujo por 3.5 h. Fue agregada agua a la mezcla de reacción y la mezcla fue extraída con éter dietílico. La capa de éter dietílico fue lavada con agua y solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:acetato de etilo=2.5:1) para producir el compuesto de título como un aceite amarillo (1.58 g).

Etapa 3

Producción de ácido 1-(1-benciloxicarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carboxílico

1-(1-Benciloxicarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carboxilato de metilo (1,58 g) producido en la etapa anterior fue disuelto en tetrahidrofurano (5 ml), metanol (5 ml) y agua (10 ml), fue agregado hidróxido de litio monohidrato (834 mg) y la mezcla fue agitada a 50°C por 6 h. La mezcla de reacción

fue concentrada bajo presión reducida, fue agregada agua al residuo obtenido, fue acidificado con ácido clorhídrico 2N, y fue extraída con acetato de etilo. La capa de acetato de etilo, fue lavada con solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. Al residuo obtenido fueron agregados éter dietílico y n-hexano, y el sólido precipitado fue recolectado por filtración, y secado para producir el compuesto de título como un sólido amorfo blanco (1.27 g).

Etapa 4

Producción de 1-[1-(1-benciloxicarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-3-(piridin-3-il)pirrolidina

Ácido 1-(1-benciloxicarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carboxílico (800 mg) producido en la etapa anterior, 1-hidroxibenzotriazol (332 mg) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida (498 mg) fueron disueltos en N,N-dimetilformamida (10 ml), y la mezcla fue agitada por 15 min. A la solución obtenida le fueron agregados 3-(piridin-3-il)pirrolidina (330 mg) y 4-dimetilaminopiridina (cantidad catalizadora) y la mezcla fue agitada toda la noche a la temperatura ambiente. La mezcla de reacción fue concentrada bajo presión reducida, fue agregada agua al residuo obtenido, y la mezcla fue extraída con acetato de etilo. La capa de éter etílico fue lavada con solución salina, fue secada sobre el sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=11:1) para producir el compuesto del título como un sólido amorfo blanco (1.06 g).

Etapa 5

Producción de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-3-(piridin-3-il)pirrolidina

1-[1-(1-Benciloxicarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-3-(piridin-3-il)pirrolidina (970 mg) producido en la etapa anterior fue disuelto en metanol (12 ml), paladio carbono al 10% (50% contenido de agua) (200 mg) fue agregado, y la mezcla fue agitada bajo una atmósfera de hidrógeno por 2.5 h. El catalizador fue eliminado por filtración, y el filtrado fue concentrado bajo presión reducida. El residuo obtenido fue purificado por cromatografía (alúmina neutra) (cloroformo:metanol=7:1) para producir el compuesto del título como un sólido amorfo blanco (718 mg).

Ejemplo 2

Producción de clorhidrato de 5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Etapa 1

Producción de (S)-3-acetil-4-isopropi-5.5-difeniloxazolidin-2-ona

Bajo una atmósfera de argón, fue suspendido (S)-4-isopropil-5.5-difeniloxazolidin-2-ona (1.56 g) en tetrahidrofurano (22 ml), y fue agregada solución de n-butillitio/n-hexano 1.6M (3.64 ml) bajo un baño de hielo. Después de 10 min, fue agregado cloruro de acetilo (0.47 ml), y la mezcla fue agitada toda la noche mientras se permite que la mezcla retorne gradualmente a la temperatura ambiente. Una solución saturada de cloruro de amonio en agua fue agregada a la mezcla de reacción, y la mezcla fue concentrada bajo presión reducida. Fue agregada agua al residuo obtenido y la mezcla fue extraída con acetato de etilo. La capa de acetato de etilo fue lavada con ácido clorhídrico 1N, fue lavada con agua, luego con solución saturada de carbonato ácido de sodio y agua, y fue secada sobre sulfato de magnesio anhidro. La capa de acetato de etilo fue concentrada bajo presión

reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:acetato de etilo=4:1) para producir el compuesto del título como cristales blancos (1.69 g).

Etapa 2

Producción de (S)-4-isopropil-3-[(S)-4-nitro-3-(2-trifluorometil-fenil)butiril]-5.5-difeniloxazolidin-2-ona

(S)-3-Acetil-4-isopropil-5.5-difeniloxazolidin-2-ona (4.74 g) producida en la etapa anterior fue disuelta en diclorometano (73 ml) bajo una atmósfera de argón, y fueron agregados tetracloruro de titanio (3.17 ml) y N,N-diisopropiletilamina (3.06 ml) a -78°C. La mezcla fue calentada gradualmente a 0°C en 30 min, de nuevo enfriada a -78°C y fue agregada una solución 1-[(E)-2-nitrovinil]-2-trifluorometilbenceno (3.50 g) en diclorometano (27 ml). Fue agregado tetracloruro de titanio (3.17 ml) y, 2 h después, fue agregada una solución saturada de cloruro de amonio en agua a la mezcla de reacción. La mezcla fue extraída con acetato de etilo, y la capa de acetato de etilo fue lavada con ácido clorhídrico 1N, con agua, con una solución saturada de carbonato ácido de sodio en agua y con agua, y secada sobre sulfato de magnesio anhidro. La mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:acetato de etilo=5:1) y cristalizado con éter dietílico:n-pentano para producir el compuesto del título como cristales blancos (2.62 g).

Etapa 3

Producción de (S)-4-(2-trifluorometilfenil)pirrolidin-2-ona

Fueron agregados etanol (35 ml) y acetato de etilo (35 ml) a (S)-4-

isopropil-3-[(S)-4-nitro-3-(2-trifluorometilfenil)butiril]-5.5-difeniloxazolidin-2-ona (2.51 g) producida en la etapa anterior, y fue agregado níquel de Raney (50% de agua) (2.8 g). Después de revolver toda la noche bajo una atmósfera de hidrógeno, el material insoluble fue filtrado a través de celite, y el filtrado fue concentrado bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol = 20:1) para producir el compuesto del título como cristales blancos (850 mg).

Etapa 4

Producción de (S)-3-(2-trifluorometilfenil)pirrolidina

A (S)-4-(2-trifluorometilfenil)pirrolidin-2-ona (803 mg) producida en la etapa anterior le fue agregado tetrahidrofurano (7 ml), y fue agregado hidruro de litio aluminio (200 mg). Después de calentar bajo reflujo durante 1.5 h, fueron agregados agua (0.2 ml), solución de hidróxido de sodio 4N en agua (0.2 ml) y agua (0.4 ml) bajo un baño de hielo. Fue agregado sulfato de magnesio anhidro, el material insoluble fue filtrado a través de celite, y el filtrado fue concentrado bajo presión reducida para producir el compuesto del título como un aceite pálido-amarillo (722 mg).

$[\alpha]^{25}D$=+23.9 (c=0.504; EtOH)

Etapa 5

Producción de 1-[1-(1-benciloxicarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fueron disueltos ácido 1-(1-Benciloxicarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carboxílico (235 mg) producido en el ejemplo 1, etapa 3, 1-hidroxibenzotriazol (127 mg) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida (159 mg) en N,N-dimetilformamida (6 ml), y la mezcla fue agitada por 15

min. A la solución obtenida fue agregado (S)-3-(2-trifluorometilfenil)pirrolidina (151 mg) producida en la etapa anterior y 4-dimetilaminopiridina (78 mg), y la mezcla fue agitada toda la noche a temperatura ambiente. La mezcla de reacción fue concentrada bajo presión reducida, fue agregada agua al residuo obtenido, y la mezcla fue extraída con acetato de etilo. La capa del acetato de etilo fue lavada con agua, con sulfato ácido de potasio 1N en agua, con solución saturada de carbonato ácido de sodio en agua y con salmuera, fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (acetato de etilo:metanol=40:1) para producir el compuesto del título como un sólido amorfo blanco (287 mg).

Etapa 6

Producción de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

1-[1-(1-Benciloxicarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (2.0 g) producida en la etapa anterior fue disuelta en metanol (14 ml), fue agregado hidróxido de carbono paladio (0.2 g), y la mezcla fue agitada bajo una atmósfera de hidrógeno durante 15 h. El catalizador fue eliminado por filtración con celite, y el filtrado fue concentrado bajo presión reducida. El residuo fue disuelto en metanol (6.4 ml), y fue agregada una solución 4N de ácido clorhídrico en acetato de etilo (1.32 ml). La mezcla fue concentrada bajo presión reducida, y cristalizada con acetato de etilo+éter diisopropílico para producir el compuesto del título como cristales blancos (1.45 g).

Etapa 7

(S)-3-(2-trifluorometilfenil)pirrolidina producida en la etapa 4 indicado precedentemente y un clorhidrato de la misma también pueden ser producidos de

acuerdo a las etapas siguientes.

Etapa 7-1

Producción de 2-[(S)-2-nitro-1-(2-trifluorometilfenil)etil]malonato de dimetilo

Fue agregado tolueno (40 ml) a 1-((E)-2-nitrovinil)-2-trifluorometilbenceno (4.34 g), y malonato de dimetilo (3.4 ml) y 1-(3.5-bis-trifluorometilfenil)-3-((1S.2S)-2-dimetilaminociclohexil)-tiourea (413 mg) descrita en WO2005/000803 y "J. Am. Chem. Soc.", 2005, 127, 119-125 fueron agregados bajo un baño de hielo. La mezcla fue agitada bajo un baño de hielo durante 24 h. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo fue cristalizado de 2-propanol para producir el compuesto del título (5.31 g) como cristales blancos.

Esta reacción también puede realizarse usando catalizadores descritos en "J. Am. Chem. Soc.", 1999, 121, 10215-10216, "J. Am. Chem. Soc.", 2005, 127, 9958-9959, "J. Am. Chem. Soc.", 2006, 128, 1454-1455 y similar, en lugar de 1-(3.5-bis-trifluorometilfenil)-3-((1S.2S)-2-dimetilaminociclohexil)-tiourea.

Etapa 7-2

Producción de (S)-2-oxo-4-(2-trifluorometilfenil)pirrolidin-3-carboxilato de metilo

2-[(S)-2-nitro-1-(2-trifluorometilfenil)etil]malonato de dimetilo (4.0 g) producido en la etapa anterior fue agregado a una suspensión de níquel Raney (2.0 g) en tetrahidrofurano (10 ml)/metanol (10 ml), y la mezcla fue agitada bajo 3.616 kg/cm^2 de hidrógeno a temperatura ambiente durante 24 h. Los materiales insolubles fueron eliminados por filtración a través de celite. El filtrado y el lavado fueron combinados y concentrados bajo presión reducida. El tolueno fue agregado al

residuo, y la mezcla fue lavada con solución al 10% de carbonato de potasio en agua y con agua, y la capa orgánica fue concentrada bajo presión reducida. El residuo fue cristalizado de tolueno+n-hexano para producir el compuesto del título (2.38 g) como cristales blancos.

Esta reacción también puede ser realizada usando carbono paladio en lugar de níquel Raney con un ácido tal como ácido acético, ácido tosílico, ácido mesílico y/o algo similar.

Etapa 7-3

Producción de (S)-4-(2-trifluorometilfenil)pirrolidin-2-ona

El metanol (3.8 ml) fue agregado a (S)-2-oxo-4-(2-trifluorometilfenil)pirrolidin-3-carboxilato de metilo (1.0 g) producido en la etapa anterior, fue agregado además una solución 1N de hidróxido de sodio en agua (3.8 ml), y la mezcla fue agitada a 65°C durante 1 h. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo obtenido fue acidificado con ácido clorhídrico 1N bajo un baño de hielo y fue extraído dos veces con acetato de butilo. Las capas orgánicas fueron combinadas, lavadas con solución salina, fueron secadas sobre sulfato de magnesio anhidro, y concentradas bajo presión reducida. Fue agregado acetato de butilo (10 ml) al residuo, y la mezcla fue agitada toda la noche a 100°C. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo fue cristalizado con n-hexano para producir el compuesto del título (667 mg) como cristales blancos.

Etapa 7-4

Producción de clorhidrato de (S)-3-(2-trifluorometilfenil)pirrolidina

A una solución de (S)-4-(2-trifluorometilfenil)pirrolidin-2-ona (22.9 g) producida en la etapa anterior en THF (100 ml) fue agregado lentamente una

solución 1M de hidruro de aluminio litio en THF (100 ml) bajo una atmósfera de argón a 85°C durante 1 h, y la mezcla fue agitada a la misma temperatura durante 1 h. Después de permitir enfriar, fue agregada una solución acuosa al 50% de sal de Rochelle bajo un baño de hielo, y la mezcla fue dividida entre agua y acetato de etilo. La capa orgánica fue separada y concentrada bajo presión reducida. El residuo fue dividido entre agua y acetato de etilo, y la capa orgánica fue secada sobre sulfato de magnesio anhidro y fue concentrada bajo presión reducida. El acetato de etilo (60 ml) fue agregado al residuo, fue agregada una solución 4N de ácido clorhídrico en acetato de etilo (37.5 ml) bajo un baño de hielo, y la mezcla fue agitada a temperatura ambiente. Los cristales precipitados fueron recolectados por filtración para dar el compuesto del título (20.6 g) como cristales blancos.

$[\alpha]^{25}D$ = +10.3 (c = 0.55; MeOH)

Ejemplo 3

Producción de 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina

1-[5-Ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-3-(piridin-3-il)pirrolidina (100 mg) producida en el ejemplo 1, etapa 5 fue disuelta en cloroformo (2 ml), fueron agregados trietilamina (38 ml) y 2-fluorofenilisocianato (34 ml), y la mezcla fue agitada a temperatura ambiente durante 3 h. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=11:1) para producir el compuesto del título como un sólido amorfo blanco (111 mg).

Ejemplo 4

Producción de 1-[1-(1-carbamoilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

1-[5-Ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (1.0 g) producida por un método similar al del ejemplo 1, etapa 5 fue disuelta en ácido acético (3 ml) y agua (6 ml), y fue agregada lentamente una solución acuosa (6 ml) de cianuro de sodio (300 mg) a temperatura ambiente. La mezcla fue agitada a temperatura ambiente durante 6 h mientras fue agregado cianuro de sodio (750 mg total) a los mismos. La mezcla fue extraída con acetato de etilo, y la capa de acetato de etilo fue lavada con ácido clorhídrico 1N, con agua, con solución saturada de carbonato ácido de sodio en agua, con agua y solución salina, y fue secada sobre sulfato de magnesio anhidro. La mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=10:1). Fue agregado éter dietílico (10 ml), y la mezcla fue agitada a temperatura ambiente durante 2 h. El sólido precipitado fue reunido por filtración y secado para producir el compuesto del título como cristales blancos (581 mg).

Ejemplo 5

Producción de 1-{1-[1-(2-carboxifenilcarbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Clorhidrato de 1-[5-Ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (703 mg) del ejemplo 2 fue suspendida en cloroformo (7 ml), y fue agregado trietilamina (0.23 ml). Bajo un baño de hielo, fue

agregado 2-metoxicarbonilfenilisocianato (292 mg), y la mezcla fue agitada a temperatura ambiente durante 2 h. La mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=30:1) para dar 1-{5-ciclopropil-1-[1-(2-metoxicarbonilfenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (992 mg) como un sólido amorfo blanco.

La 1-{5-ciclopropil-1-[1-(2-metoxicarbonilfenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (244 mg) obtenida fue disuelta en tetrahidrofurano (0.4 ml) y metanol (0.2 ml); fue agregada una solución 4N de hidróxido de sodio en agua (0.4 ml), y la mezcla fue agitada a 60°C durante 4 hs. La mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue disuelto en agua. Bajo un baño de hielo, la mezcla fue acidificada con ácido clorhídrico 2N y extraída con cloroformo. La capa de cloroformo fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. Fue agregado n-hexano al residuo para dar precipitación de cristal. El cristal obtenido fue lavado con n-hexano y secado bajo presión reducida para producir el compuesto del título como un sólido amorfo blanco (181 mg).

Ejemplo 6

Producción de 1-{5-ciclopropil-1-[1-(2-hidroximetilfenilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

1-{5-Ciclopropil-1-[1-(2-metoxicarbonilfenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (213 mg) obtenida en el ejemplo 5 fue disuelta en tetrahidrofurano (2 ml) y etanol (2 ml), y cloruro de litio (30

mg) y el borohidruro de sodio (26 mg) fue agregado bajo un baño de hielo. La mezcla fue agitada toda la noche a temperatura ambiente. El material insoluble precipitado fue recolectado por filtración, y lavado con cloroformo. El filtrado y lavado fueron combinados, y la mezcla fue lavada con agua, con solución saturada de cloruro de sodio en agua, secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=30:1) para producir el compuesto del título como un sólido amorfo blanco (109 mg).

Ejemplo 7

Producción de 1-{5-ciclopropil-1-[1-(1-hidroximetilciclopropilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 5, el compuesto del título fue obtenido como un sólido amorfo blanco (530 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina (1.07 g) del ejemplo 2.

Ejemplo 8

Producción de 1-{5-ciclopropil-1-[1-(2-hidroxietilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 5, el compuesto del título fue obtenido como un sólido amorfo blanco (202 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina (206 mg) del ejemplo 2.

Ejemplo 9

Producción de 1-{5-ciclopropil-1-[1-(2-hidroxi-1.1-dimetiletilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 5, el compuesto del título fue obtenido como un sólido amorfo blanco (341 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina (350 mg) del ejemplo 2.

Ejemplo 10

Producción de 1-{1-[1-(2-acetilaminoetilcarbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Etapa 1

Producción de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Al clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (5.04 g) del ejemplo 2 fue agregado cloroformo (50 ml), N,N-diisopropiletilamina (4.68 ml) y cloroformato de 4-nitrofenilo (2.39 g) fue agregado bajo un baño de hielo, y la mezcla fue agitada a temperatura ambiente durante 1 h. La mezcla fue concentrada bajo presión reducida, acidificada con ácido clorhídrico 1N, y fue extraída con acetato de etilo. La capa del acetato de etilo fue lavada con agua y solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=20:1) para producir el compuesto del título como una sustancia amorfa color amarillo pálido (5.41 g).

Etapa 2

Producción de 1-{1-[1-(2-acetilaminoetilcarbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

1-{5-Ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) producida en la etapa anterior fue disuelta en N-metilpirrolidona (1 ml), y fue agregado N-(2-aminoetil)-acetamida (96 ml). La mezcla fue agitada toda la noche a 80°C. Después de dejarlo enfriar, fue agregada solución acuosa al 10% de carbonato de potasio, y la mezcla

fue extraída con acetato de etilo. La capa de acetato de etilo fue lavada con agua, con ácido clorhídrico 1N y con agua, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=15:1) para producir el compuesto del título como un sólido amorfo blanco (65 mg).

Ejemplo 11

Producción de clorhidrato de 1-{1-[1-(2-aminoetilcarbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

1-{5-Ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) producida en el ejemplo 10, etapa 1 y (2-aminoetil)carbamato de t-butilo (160 mg) fueron disueltos en acetonitrilo (1 ml), y la mezcla fue agitada toda la noche y fue calentada bajo reflujo. La mezcla fue diluída con cloroformo, y la mezcla fue lavada con agua, con solución acuosa saturada de carbonato ácido de potasio, con agua y con solución salina, y fue secado sobre sulfato de magnesio anhidro. La mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=10:1). El sólido amorfo obtenido fue disuelto en acetato de etilo (1 ml), y fue agregado solución de ácido clorhídrico 4N en acetato de etilo (4 ml). El sólido precipitado fue separado por filtración y secado para producir el compuesto del título como un sólido amorfo blanco (111 mg).

Ejemplo 12

Producción de 1-{5-ciclopropil-1-[1-(1.1-dioxotiomorfolina-4-carbonil)-piperidin-

4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina

1-{5-Ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (250 mg) producida en el ejemplo 10, etapa 1, y tiomorfolina (0.13 ml) fueron disueltos en N-metilpirrolidona (1 ml), y la mezcla fue agitada toda la noche a 100°C. Después de permitir el enfriado, la mezcla fue diluída con éter dietílico, fue lavada con agua, solución acuosa 5% de carbonato de potasio y solución salina, y fue secada sobre sulfato de sodio anhidro. La mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (acetato de etilo:metanol=30:1) para dar 1-{5-ciclopropil-1-[1-(tiomorfolina-4-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina como un sólido amorfo blanco (224 mg). Esto fue disuelto en cloroformo (4 ml), y ácido m-cloroperbenzoico (319 mg) fue agregado bajo un baño de hielo. La mezcla fue agitada por 3 h mientras le fue permitido volver gradualmente a la temperatura ambiente. Se agregaron solución acuosa saturada de tiosulfato de sodio y solución acuosa saturada de carbonato ácido de sodio, y la mezcla fue extraída con cloroformo. La capa del cloroformo fue lavada con solución salina y secada sobre sulfato de sodio anhidro. La mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (acetato de etilo:metanol=30:1) para producir de ésta manera el compuesto del título como un sólido amorfo blanco (198 mg).

Ejemplo 13

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(2-dimetilaminoetil-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-

trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 10 el compuesto del título fue obtenido como un sólido amorfo amarillo (130 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 14

Producción de 1-{5-ciclopropil-1-[1-(4-hidroxipiperidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina

Por un método similar al de Ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (176 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 15

Producción de 1-{1-[1-(azetidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por medio de un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (150 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 16

Producción de 1-{5-ciclopropil-1-[1-(3-hidroxipirrolidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (175 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 17

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(2-piperidin-1-il-etilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al de Ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (170 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 18

Producción de 1-{5-ciclopropil-1-[1-(4.4-difluoropiperidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (132 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 19

Producción de 1-{5-ciclopropil-1-[1-(3.3-difluoropirrolidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (152 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 20

Producción de 1-{5-ciclopropil-1-[1-(3-hidroxiazetidin-1-carbonil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (158 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 21

Producción de 1-(5-ciclopropil-1-{1-[(R)-3-hidroxipirrolidin-1-carbonil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (171 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 22

Producción de 1-(5-ciclopropil-1-{1-[(S)-3-hidroxipirrolidin-1-carbonil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (172 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 23

Producción de 1-(5-ciclopropil-1-{1-[(S)-2-hidroxi-1-metietilcarbamoil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo amarillo (60 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 24

Producción de 1-{5-ciclopropil-1-[1-(4-hidroximetilpiperidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (94 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (150 mg).

Ejemplo 25

Producción de 1-{1-[1-(4-carboxipiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al de Ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (65 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (172 mg).

504

Ejemplo 26

Producción de 1-{5-ciclopropil-1-[1-(3-oxopiperazin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (143 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 27

Producción de 1-(5-ciclopropil-1-{1-[(S)-2-hidroximetilpirrolidin-1-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo amarillo (150 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 28

Producción de 1-{5-ciclopropil-1-[1-(3-hidroximetilazetidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo amarillo (178 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 29

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(4-metilpiperazin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (66 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (150 mg).

506

Ejemplo 30

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(4-isopropilpiperazin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 10, el compuesto del titulo fue obtenido como un sólido amorfo blanco (50 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (150 mg).

Ejemplo 31

Producción de 1-{1-[1-(4-acetilpiperazin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (56 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (150 mg).

Ejemplo 32

Producción de 1-(5-ciclopropil-1-{1-[(R)-3-hidroxipiperidin-1-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo amarillo (170 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg).

Ejemplo 33

Producción de 1-{1-[1-(4-carbamoilpiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (108 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (150 mg).

508

Ejemplo 34

Producción de 1-{1-[1-(3-carbamoilazetidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (93 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (171 mg).

Ejemplo 35

Producción de clorhidrato de 1-{1-[1-(4-aminopiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 11, el compuesto del título fue obtenido como un sólido amorfo blanco (302 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (478 mg).

509

Ejemplo 36

Producción de clorhidrato de 1-{1-[1-(3-aminopirrolidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)] pirrolidina

Por un método similar al del ejemplo 11, el compuesto del título fue obtenido como un sólido amorfo beige pálido (635 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (478 mg).

Ejemplo 37

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(piperidin-4-il-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 11, el compuesto del título fue obtenido como un sólido amorfo blanco (59 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (478 mg).

Ejemplo 38

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(4-dimetilamino-piperidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 12, el compuesto del título fue obtenido como un sólido amorfo blanco (74 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (478 mg).

Ejemplo 39

Producción de 1-{1-[1-(4-acetilaminopiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 12, el compuesto del título fue obtenido como un sólido amorfo blanco (100 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (478 mg).

Ejemplo 40

Producción de 1-{1-[1-(3-acetilaminopirrolidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 12, el compuesto del título fue obtenido como un sólido amorfo blanco (127 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (478 mg).

Ejemplo 41

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(3-dimetilaminopirrolidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 12, el compuesto del título fue obtenido como un sólido amorfo beige pálido (141 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (478 mg).

512

Ejemplo 42

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(1-metilpiperidin-4-il-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 12, el compuesto del título fue obtenido como un sólido amorfo blanco (116 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (181 mg).

Ejemplo 43

Producción de 1-{1-[1-(1-acetilpiperidin-4-il-carbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 12, el compuesto del título fue obtenido como un sólido amorfo blanco (41 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (181 mg).

Ejemplo 44

Producción de 1-{5-ciclopropil-1-[1-(4-oxopiperidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 12, el compuesto del título fue obtenido como un sólido amorfo blanco (155 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (540 mg).

Ejemplo 45

Producción de 1-{1-[1-(3-acetilaminoazetidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 12, el compuesto del título fue obtenido como un sólido amorfo blanco (68 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (90 mg).

514

Ejemplo 46

Producción de 1-{5-ciclopropil-1-[1-(3-oxopirrolidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 12, el compuesto del título fue obtenido como un sólido amorfo blanco (155 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (300 mg).

Ejemplo 47

Producción de 1-{5-ciclopropil-1-[1-(2.2.2-trifluoroetilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Etapa 1

Producción de (2.2.2-trifluoroetil)carbamato 4-nitrofenilo

2.2.2-Trifluoroetilamina (392 mg) fue disuelta en cloroformo (4 ml), y piridina (0.35 ml) y cloroformato de 4-nitrofenilo (2.39 g) fue agregado bajo un baño de hielo. La mezcla fue agitada a temperatura ambiente durante 1 h. La mezcla fue concentrada bajo presión reducida, fue agregada agua al residuo obtenido, y la mezcla fue extraída con acetato de etilo. La capa de acetato de etilo fue lavada con ácido clorhídrico 1N y con agua, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. Fue agregado éter diisopropílico al residuo obtenido, y el sólido precipitado fue separado por filtración y fue secado para producir el compuesto del título como un sólido blanco (501 mg).

Etapa 2

Producción de 1-{5-ciclopropil-1-[1-(2.2.2-trifluoroetilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

(2.2.2-trifluoroetil)carbamato de 4-Nitrofenilo (113 mg) producido en la etapa anterior y el clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2 fueron disueltos en piridina (1 ml), y la mezcla fue agitada a 80°C durante 2 h. Después permitir enfriamiento, fue agregado tolueno y la mezcla fue concentrada bajo presión reducida. Solución al 10% de carbonato de potasio en agua fue agregada, y la mezcla fue extraída con acetato de etilo. La capa del acetato de etilo fue lavada con solución al 10% de carbonato de potasio en agua, con agua, con ácido clorhídrico 1N y con agua de nuevo, secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=15:1) para producir el compuesto del título como un sólido amorfo amarillo pálido (162 mg).

Ejemplo 48

Producción de 1-{5-ciclopropil-1-[1-(3.3.4.4-tetrafluoropirrolidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 47, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (138 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (468 mg) del ejemplo 2.

Ejemplo 49

Producción de 1-(5-ciclopropil-1-{1-[(S)-1-hidroximetil-2-metilpropilcarbamoil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 47, el compuesto del título fue obtenido como un sólido amorfo blanco (166 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (250 mg) del ejemplo 2.

Ejemplo 50

Producción de 1-(1-{1-[(S)-1-bencil-2-hidroxietilcarbamoil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 47, el compuesto del título fue obtenido como un sólido amorfo blanco (140 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (300 mg) del ejemplo 2.

Ejemplo 51

Producción de 1-(5-ciclopropil-1-{1-[(S)-2-hidroxi-1-feniletilcarbamoil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 47, el compuesto del título fue obtenido como un sólido amorfo blanco (170 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (300 mg) del ejemplo 2.

Ejemplo 52

Producción de 1-(5-ciclopropil-1-{1-[(S)-1-hidroximetil-3-metil-butilcarbamoil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 47, el compuesto del título fue obtenido como un sólido amorfo amarillo (256 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (250 mg) del ejemplo 2.

Ejemplo 53

Producción de 1-{5-ciclopropil-1-[1-(2-hidroxifenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 47, el compuesto del título fue obtenido como un sólido amorfo blanco (125 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2.

Ejemplo 54

Producción de 1-{5-ciclopropil-1-[1-(1-hidroximetilciclopentil-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 47, el compuesto del titulo fue obtenido como un sólido amorfo blanco (92 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2.

Ejemplo 55

Producción de 1-[1-(1-bencensulfonilaminocarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fue agregado cloroformo (3 ml) a clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (250 mg) del ejemplo 2, fueron agregados trietilamina (81 ml) y toluensulfonilisocianato (78 ml) y la mezcla fue agitada por 2 h. La mezcla fue concentrada bajo presión reducida, fue agregada agua al residuo obtenido, y la mezcla fue extraída con cloroformo. La capa de cloroformo fue lavada con solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=10:1). El sólido obtenido fue recristalizado del acetato de etilo para producir el compuesto del título como un sólido amarillo pálido (40 mg).

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Ejemplo 56

Producción de 1-[5-ciclopropil-1-(1-metansulfonilaminocarbonilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 55, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (200 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (500 mg) del ejemplo 2.

Ejemplo 57

Producción de 1-[5-ciclopropil-1-(1-metoxicarbonilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2 fue suspendido en cloroformo (2.0 ml), y carbonato de potasio (177 mg) fue agregado bajo un baño de hielo. El cloroformato de metilo (49.4 µl) fue agregado, y a la mezcla se le permite retornar a la temperatura ambiente y fue agitada por 1.5 h. El cloroformato de metilo (49.4 ml) fue agregado adicionalmente, y la mezcla fue agitada a temperatura ambiente durante 15.5 h. Fue agregada una solución saturada de carbonato ácido de sodio en agua a la mezcla de reacción, y la mezcla fue extraída 3 veces con acetato de etilo. La capa orgánica fue lavada con agua y solución salina, fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=30:1) para producir el compuesto del título como un sólido amorfo blanco (210 mg).

Ejemplo 58

Producción de 1-{5-ciclopropil-1-[1-(2-hidroxietoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 57, el compuesto del título fue obtenido como un sólido amorfo blanco (214 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)3-(2-trifluorometilfenil)]-pirrolidina (300 mg) del ejemplo 2.

Ejemplo 59

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(2-dimetilaminoetoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (166 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (300 mg).

Ejemplo 60

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(2-piperidin-1-il-etoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido como un sólido amorfo blanco (219 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (300 mg).

Ejemplo 61

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(piperidin-4-il-oxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 11, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (53 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (102 mg).

Ejemplo 62

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(1-metilpiperidin-4-il-oxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 12, el compuesto del título fue obtenido como un sólido amorfo blanco (64 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (124 mg).

Ejemplo 63

Producción de 1-{1-[1-(1-acetilpiperidin-4-il-oxicarbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 12, el compuesto del título fue obtenido como un sólido amorfo blanco (65 mg) de 1-{5-ciclopropil-1-[1-(4-nitrofenoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (122 mg).

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Ejemplo 64

Producción de 1-[1-(1-ciclopropancarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fueron agregados cloroformo (5 ml) y trietilamina (0.13 ml) a clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2 y fue agregado cloruro de ciclopropancarboxílico (0.047 ml) bajo un baño de hielo. Después de agitar toda la noche a temperatura ambiente, el solvente fue eliminado bajo presión reducida, fue agregada agua al residuo obtenido, y la mezcla fue extraída con acetato de etilo. La capa de acetato de etilo fue lavada con solución acuosa saturada de carbonato ácido de sodio en agua y solución salina, y fue secado sobre sulfato de sodio anhidro. La mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (acetato de etilo:metanol=10:1) para producir el compuesto del título como un sólido amorfo blanco (170 mg).

Ejemplo 65

Producción de 1-{5-ciclopropil-1-[1-(2-hidroxiacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fueron agregados cloroformo (5 ml) y trietilamina (0.16 ml) a clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (250 mg) del ejemplo 2 y cloruro de acetoxiacetilo (0.069 ml) fue agregado bajo un baño de hielo. Después de agitar toda la noche a temperatura ambiente, la mezcla fue concentrada bajo presión reducida, fue

agregada agua al residuo obtenido, y la mezcla fue extraída con acetato de etilo. La capa de acetato de etilo fue lavada con solución saturada de carbonato ácido de sodio en agua y solución salina, y secada sobre sulfato de sodio anhidro. La mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (acetato de etilo:metanol=10:1). El sólido amorfo obtenido fue disuelto en tetrahidrofurano (2 ml), metanol (2 ml) y agua (4 ml), y fue agregado hidróxido de litio monohidrato (103 mg). La mezcla fue agitada a 60°C durante 4 h. La mezcla fue concentrada bajo presión reducida, fue agregada solución acuosa al 5% de sulfato ácido de potasio al residuo obtenido, y la mezcla fue extraída con acetato de etilo. La capa de acetato de etilo fue lavada con agua y solución salina, y fue secada sobre sulfato de sodio anhidro. La mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (acetato de etilo:metanol=20:1) para producir el compuesto del título como un sólido amorfo blanco (30 mg).

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Ejemplo 66

Producción de 1-(5-ciclopropil-1-{1-[1-(4-fluorofenil)-ciclopropancarbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (193 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2.

Ejemplo 67

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(2-dimetilaminoacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (217 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2.

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Ejemplo 68

Producción de 1-{1-[1-(2-acetilaminoacetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido como un sólido amorfo beige pálido (119 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)] pirrolidina (200 mg) del ejemplo 2.

Ejemplo 69

Producción de 1-{5-ciclopropil-1-[1-(1-metilciclopropancarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (178 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2.

Ejemplo 70

Producción de 1-{1-[1-(2-acetilamino-2-metilpropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido como un sólido amorfo beige pálido (94 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]

pirrolidina (200 mg) del ejemplo 2.

Ejemplo 71

Producción de 1-(1-{1-[(S)-2-acetilaminopropionil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido como un sólido amorfo blanco (183 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2.

Ejemplo 72

Producción de 1-(1-{1-[(S)-2-acetilamino-3-metilbutiril]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (212 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2.

Ejemplo 73

Producción de 1-{5-ciclopropil-1-[1-(3.3.3-trifluoropropionil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (151 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (150 mg) del ejemplo 2.

Ejemplo 74

Producción de 1-(5-ciclopropil-1-{1-[(S)-5-oxopirrolidin-2-carbonil]-piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido como un sólido amorfo blanco (127 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina (200 mg) del ejemplo 2.

Ejemplo 75

Producción de 1-{1-[1-(3-acetilaminopropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (263 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (355 mg) del ejemplo 2.

Ejemplo 76

Producción de 1-{5-ciclopropil-1-[1-(3-hidroxi-2.2-dimetilpropionil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo blanco (238 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina (250 mg) del ejemplo 2.

Ejemplo 77

Producción de clorhidrato de 1-{1-[1-(2-aminoacetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (219 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2.

Ejemplo 78

1-{5-ciclopropil-1-[1-(1-hidroximetilciclopropancarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como cristales blancos (168 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina (250 mg) del ejemplo 2.

Ejemplo 79

Producción de clorhidrato de 1-{1-[1-(2-amino-2-metilpropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo amarillo castaño pálido (154 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2.

Ejemplo 80

Producción de 1-{5-ciclopropil-1-[1-(4-hidroxibutiril)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo blanco (166 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina (200 mg) del ejemplo 2.

Ejemplo 81

Producción de clorhidrato de 1-(5-ciclopropil-1-{1-[(S)-pirrolidin-2-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (569 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina del ejemplo 2 (450 mg).

Ejemplo 82

Producción de clorhidrato de 1-(5-ciclopropil-1-{1-[(S)-1-metilpirrolidin-2-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (192 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina del ejemplo 2 (450 mg).

Ejemplo 83

Producción de clorhidrato de 1-{1-[1-(3-aminopropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (414 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (355 mg) del ejemplo 2.

Ejemplo 84

Producción de clorhidrato de 1-(1-{1-[(S)-2-amino-3-metilbutiril]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo amarillo castaño pálido (182 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (150 mg) del ejemplo 2.

Ejemplo 85

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(2-metilaminoacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como sólido amorfo amarillo castaño pálido (183 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (150 mg) del ejemplo 2.

Ejemplo 86

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(piperidin-4-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo amarillo castaño pálido (478 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (404 mg) del ejemplo 2.

Ejemplo 87

Producción de 1-{5-ciclopropil-1-[1-(2-isobutirilaminoacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo amarillo castaño pálido (214 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2.

Ejemplo 88

Producción de 1-{1-[1-(2-ciclopropancarbonilaminoacetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (190 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2.

Ejemplo 89

Producción de 1-(1-{1-[(S)-1-acetilpirrolidin-2-carbonil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (189 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-

trifluorometilfenil)]pirrolidina del ejemplo 2 (450 mg).

Ejemplo 90

Producción de 1-{5-ciclopropil-1-[1-(2-metansulfonilaminoacetil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo blanco (134 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina del ejemplo 2 (152 mg).

Ejemplo 91

Producción de 1-{1-[1-(1-acetilpiperidin-4-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (145 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (404 mg) del ejemplo 2.

Ejemplo 92

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(1-metilpiperidin-4-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo amarillo castaño pálido (151 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (404 mg) del ejemplo 2.

Ejemplo 93

Producción de 1-{1-[1-(3-carbamoilpropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido como un sólido amorfo blanco (61 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina (200 mg) del ejemplo 2.

Ejemplo 94

Producción de clorhidrato de 1-[1-(1-carbamoilmetilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina.

Clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2 fue disuelto en N,N-dimetilformamida (2.5 ml), y fueron agregados carbonato de potasio (93 mg) y 2-bromoacetamida (50.7 mg). La mezcla fue agitada a temperatura ambiente durante 2 h. Fue agregada agua a la mezcla de reacción, y la mezcla fue extraída 3 veces con acetato de etilo. La capa orgánica fue lavada con agua y solución salina, fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=20:1) para dar 1-[1-(1-carbamoilmetilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (167 mg) como un sólido amorfo blanco.

1-[1-(1-Carbamoilmetilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (154 mg) obtenida en el paso anterior fue disuelta en acetato de etilo (2 ml), y fue agregado solución 4N de ácido clorhídrico en acetato de etilo (159 ml). La mezcla fue agitada por 10 min. Los cristales precipitados fueron separados por filtración y secados para producir el compuesto del título como un sólido amorfo blanco (109 mg).

Ejemplo 95

Producción de clorhidrato de 1-[5-ciclopropil-1-(1-metilcarbamoil-metilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina.

Fue disuelto clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (2.5 g) del ejemplo 2 en N,N-dimetilformamida (20 ml), y fueron agregados carbonato de potasio (1.62 g) y bromoacetato de etilo (0.98 g). La mezcla fue agitada a temperatura ambiente durante 1 h. Fue agregada agua a la mezcla de reacción, y la mezcla fue extraída dos veces con acetato de etilo. La capa orgánica fue lavada con agua y solución salina, fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=25:1) para dar 1-{5-ciclopropil-1-[1-(etoxicarbonilmetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (2.79 g) como un sólido amorfo blanco.

1-{5-Ciclopropil-1-[1-(etoxicarbonilmetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (1.4 g) obtenida en el paso anterior fue disuelta en tetrahidrofurano (5.5 ml) y metanol (2.7 ml), y fue agregada una solución 4N de hidróxido de sodio en agua (1.4 ml). La mezcla fue agitada a temperatura ambiente durante 1 h. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo obtenido fue disuelto en agua. La capa acuosa fue lavada dos veces con éter dietílico, fue ajustada a pH 5-6 con ácido clorhídrico 2N bajo un baño de hielo, y fue extraída 3 veces con cloroformo. La capa del cloroformo fue secada sobre sulfato de magnesio anhidro, fue concentrada bajo presión reducida, y n-hexano fue agregado al residuo obtenido. El sólido precipitado fue recolectado por filtración, y fue secado para dar 1-[1-(1-carboximetilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (1.17 g) como un sólido blanco.

N,N-Dimetilformamida (3.0 ml) fue agregada a 1-[1-(1-carboximetilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-

trifluorometilfenil)]pirrolidina (150 mg) obtenida en la etapa anterior, fueron agregados 1-hidroxibenzotriazol (61 mg) y el clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (76 mg), y la mezcla fue agitada a temperatura ambiente durante 1 h. Fue agregada una solución al 40% de metilamina en agua (106 ml), y la mezcla fue agitada durante 5 h, fue agregada además solución al 40% de metilamina en agua (318 ml), y la mezcla fue agitada a temperatura ambiente durante 13 h. Fue agregada agua a la mezcla de reacción, y la mezcla fue extraída con cloroformo. La capa orgánica fue lavada con solución saturada de carbonato ácido de sodio en agua, agua y solución salina, secadas sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=20:1). El sólido amorfo obtenido fue disuelto en acetato de etilo (2.0 ml), fue agregada solución 4N de ácido clorhídrico en acetato de etilo (100 ml), y la mezcla fue agitada por 10 min. Los cristales precipitados fueron separados por filtración y secados para producir el compuesto del título como un sólido amorfo blanco (16.9 mg).

Ejemplo 96

Producción de clorhidrato de 1-{1-[1-(1-carbamoil-1-metiletil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fueron disueltos cumilamina (1.1 g) y trietilamina (1.2 ml) en cloroformo (10 ml), y fue agregada una solución de bromuro de 2-bromoisobutirilo (1.0 ml) en cloroformo (2 ml) bajo un baño de hielo durante 5 min. La mezcla fue agitada a temperatura ambiente durante 15 min. La mezcla fue concentrada bajo presión reducida, fue agregado acetato de etilo al residuo obtenido, y la mezcla fue

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lavada con agua y solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El sólido blanco obtenido fue lavado con éter diisopropílico, y secado para dar 2-bromo-2-metil-N-(1-metil-1-feniletil)propilamida como un sólido blanco (1.73 g).

Fue disuelto clorhidrato de 1-[5-Ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina del ejemplo 2 en tetrahidrofurano (5.5 ml), y fue agregado hidruro de sodio al 60% (104 mg). La mezcla fue agitada a 60°C durante 1 h y a temperatura ambiente durante 5 min. Fue agregada 2-bromo-2-metil-N-(1-metil-1-feniletil)-propilamida (329 mg) producida en la etapa anterior, y la mezcla fue agitada a 60°C durante 22 h. Después de permitir enfriar, fue agregada agua a la mezcla de reacción, y la mezcla fue extraída con acetato de etilo. La capa de acetato de etilo, fue lavada con solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=20:1) para dar 1-(5-ciclopropil-1-{1-[1-metil-1-(1-metil-1-feniletilcarbamoil)etil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina como un sólido amorfo amarillo pálido (78 mg).

Fue disuelto 1-(5-ciclopropil-1-{1-[1-metil-1-(1-metil-1-feniletilcarbamoil)etil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina producida en paso anterior en ácido trifluoracético (2 ml), y la mezcla fue agitada a 80°C durante 8 h. El ácido trifluoracético (1 ml) fue agregado y la mezcla fue agitada a 80°C durante 8 h. Después de permitir enfriar, la mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue disuelto en acetato de etilo. La capa del acetato de etilo fue lavada con solución saturada de carbonato ácido de sodio en agua y solución salina, secadas sobre sulfato de

magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:acetona=4:5→cloroformo:metanol=10:1). El residuo obtenido fue disuelto en acetato de etilo (1 ml), y fue agregada una solución 4N de ácido clorhídrico en acetato de etilo (1 ml) y éter dietílico (1.5 ml). El sólido obtenido fue separado por filtración y fue secado para producir el compuesto del título como un sólido amarillo pálido (36 mg).

Ejemplo 97

Producción de clorhidrato de 1-{1-[1-(2-carbamoiletil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 94, el compuesto del título fue obtenido como un sólido amorfo blanco (149 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina (200 mg) del ejemplo 2.

Ejemplo 98

Producción de clorhidrato de 1-[5-ciclopropil-1-(1-ciclopropilmetil-piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 94, el compuesto del título fue obtenido como cristales blancos (133 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina (150 mg) del ejemplo 2.

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Ejemplo 99

Producción de clorhidrato de 1-[5-ciclopropil-1-(1-ciclopropilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 94, el compuesto del título fue obtenido como un sólido amorfo amarillo castaño pálido (144 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2.

Ejemplo 100

Producción de clorhidrato de 1-[5-ciclopropil-1-(1-dimetilcarbamoil-metilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 95, el compuesto del título fue obtenido como un sólido amorfo blanco (20 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina (2.5 g) del ejemplo 2.

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Ejemplo 101

Producción de clorhidrato de 1-[1-(1-carboximetilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

El compuesto del título fue obtenido como un sólido amorfo blanco (24 mg) de 1-[1-(1-carboximetilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (112 mg) producido en el ejemplo 95.

Ejemplo 102

Producción de clorhidrato de 1-[1-(1-carboxietilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 95, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (295 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina del ejemplo 2 (350 mg).

Ejemplo 103

Producción de clorhidrato de 1-{1-[1-(1-carbamoiletil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 95, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (146 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina del ejemplo 2 (350 mg).

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Ejemplo 104

Producción de clorhidrato de 1-{1-[1-(2-carboxi-2-metilpropil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 95, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (71 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina del ejemplo 2 (400 mg).

Ejemplo 105

Producción de clorhidrato de 1-{1-[1-(2-carbamoil-2-metilpropil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 95, el compuesto del título fue obtenido como un sólido amorfo blanco (52 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina del ejemplo 2 (400 mg).

Ejemplo 106

Producción de clorhidrato de 1-{1-[1-(1-carbamoil-ciclopropilmetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 95, el compuesto del título fue obtenido como un sólido amorfo blanco (82 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina del

ejemplo 2 (400 mg).

Ejemplo 107

Producción de clorhidrato de 1-(5-ciclopropil-1-{1-[1-(2-hidroxietil-carbamoil)ciclopropilmetil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 95, el compuesto del título fue obtenido como un sólido amorfo blanco (84 mg) de clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina del ejemplo 2 (400 mg).

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Ejemplo 108

Producción de 1-[5-ciclopropil-1-(1-trifluorometansulfonilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fue disuelto clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) del ejemplo 2 en cloruro de metileno (2.0 ml), y bajo una atmósfera de argón, la solución fue enfriada a -78°C, fueron agregados trietilamina (178 ml) y anhídrido de ácido trifluorometansulfónico (78.8 ml), y la mezcla fue agitada por 2.5 h. Fue agregado además anhídrido de ácido trifluorometansulfónico (78.8 ml) y la mezcla fue agitada por 2 h. Una solución saturada de carbonato ácido de sodio en agua fue agregada a la mezcla de reacción a -78°C, y la mezcla fue extraída con cloroformo. La capa orgánica fue lavada con ácido clorhídrico 1N, agua y solución salina, secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=20:1) para producir el compuesto del título como un amorfo amarillo (192 mg).

Ejemplo 109

Producción de 1-{5-ciclopropil-1-[1-(2.2.2-trifluoroetansulfonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 108, el compuesto del título fue obtenido como un sólido amorfo amarillo (29 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina (200 mg) del ejemplo 2.

Ejemplo 110

Producción de 1-{1-[1-(1-cianoiminoetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fue disuelto clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina del ejemplo 2 (300 mg) en cloroformo (5 ml), y fueron agregados trietilamina (97 ml) y N-cianoacetoimidato de metilo (66 ml). Después de agitar a temperatura ambiente durante 30 min y a 45°C durante 1.5 h, fueron agregados además trietilamina (97 ml) y N-cianoacetoimidato de metilo (66 ml), y la mezcla fue agitada a 45°C durante 2 h. La mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=15:1) para producir el compuesto del título como un sólido amorfo amarillo pálido (214 mg).

Ejemplo 111

Producción de 1-(1-{1-[cianoimino(metilamino)metil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Etapa 1

Producción de 1-(1-{1-[cianoimino(fenoxi)-metil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fue agregado cloroformo (5 ml) al clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina del ejemplo 2 (500 mg) y trietilamina (0.162 ml) y fue agregado N-cianocarbonimidato de difenilo (284 mg). La mezcla fue agitada por 1.5 h. La mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:acetona =1:1→2:3→1:2) para producir el compuesto del titulo como una forma amorfa amarillo pálido (575 mg).

Etapa 2

Producción de 1-(1-{1-[cianoimino(metilamino)metil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fue disuelto 1-(1-{1-[cianoimino(fenoxi)-metil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina (575 mg) producido en la etapa anterior en cloroformo (10 ml), fueron agregados clorhidrato de metilamina (81 mg) y trietilamina (0.31 ml), y la mezcla fue agitada a temperatura ambiente durante 30 min y a 55°C durante 5 h. Fueron agregados clorhidrato de Metilamina (81 mg) y trietilamina (2 ml) y la mezcla fue agitada a 55°C durante 1 h y a 60°C durante 30 min. Fue agregado además clorhidrato de metilamina (162 mg) y la mezcla fue agitada a 60°C durante 2.5 h. Después de permitir enfriar, la mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue disuelto en cloroformo, y la mezcla fue lavada con agua y solución salina, fue secadas sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue

purificado por cromatografía de gel de sílice (cloroformo:metanol=10:1) para producir el compuesto del título como un sólido amorfo blanco (242 mg).

Ejemplo 112

Producción de 1-{1-[1-(N-cianocarbamimidoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 111, el compuesto del título fue obtenido como un sólido amorfo amarillo pálido (249 mg) del clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina del ejemplo 2 (302 mg).

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Ejemplo 113

Producción de ácido 4-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoico

Etapa 1

Producción de 1-[1-(4-etoxicarbonilfenil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carboxilato de ter-butilo

Fueron suspendidos 2-ciclopropilcarbonil-3-dimetilaminoacrilato de ter-butilo (1.12 g) producido por un método similar al del ejemplo 1, etapa 1 y clorhidrato del 4-(4-hidrazinopiperidin-1-il)benzoato de etilo (692 mg) producido por método conocido en etanol (15 ml). Fue agregado trietilamina (0.81 ml) a la suspensión obtenida, y la mezcla fue agitada toda la noche bajo reflujo. La mezcla de reacción fue concentrada bajo presión reducida, fue agregada agua al residuo obtenido, y la mezcla fue extraída con acetato de etilo. La capa del acetato de etilo fue lavada con agua y solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:acetato de etilo=3:1) para producir el compuesto del título como un aceite amarillo (673 mg).

Etapa 2

Producción de ácido 1-[1-(4-etoxicarbonilfenil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carboxílico

Fue disuelto 1-[1-(4-etoxicarbonilfenil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carboxilato de ter-butilo (673 mg) producido en la etapa anterior en cloroformo (4 ml), fue agregado ácido trifluoracético (4 ml) bajo un baño de hielo, y la mezcla fue agitada a 40°C durante 2 h. La mezcla de reacción fue concentrada bajo

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presión reducida, fue agregada agua al residuo obtenido, y la mezcla fue extraída con acetato de etilo. La capa del acetato de etilo fue lavada con agua y solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. Al residuo obtenido fueron agregados éter dietílico y n-hexano, y el sólido precipitado fue separado por filtración y fue secado para producir el compuesto del título como un sólido blanco (556 mg).

Etapa 3

Producción de 5-ciclopropil-1-{1-[1-(4-etoxicarbonilfenil)piperidin-4-il]-1H-pirazol-4-carbonil}-{3-(2-trifluorometilfenil)}pirrolidina

Fueron disueltos ácido 5-ciclopropil-1-[1-(4-etoxicarbonilfenil)-piperidin-4-il]-1H-pirazol-4-carboxílico (550 mg) producido en la etapa anterior, 1-hidroxibenzotriazol (285 mg) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida (357 mg) en N,N-dimetilformamida (8 ml). Fue agregado 3-(2-trifluorometilfenil)pirrolidina (308 mg) a la solución obtenida y la mezcla fue agitada toda la noche a temperatura ambiente. Fue agregada agua a la mezcla de reacción, y la mezcla fue extraída con acetato de etilo. La capa del acetato de etilo fue lavada con una solución saturada de carbonato ácido de sodio en agua y solución salina, secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (acetato de etilo) para producir el compuesto del título como un sólido amorfo blanco (757 mg).

Etapa 4

Producción de ácido 4-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)-pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoico

1-{1-[1-(4-Etoxicarbonilfenil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-{3-(2-trifluorometilfenil)}pirrolidina (720 mg) producido en la etapa anterior

fue disuelto en tetrahidrofurano (3 ml) y metanol (1.5 ml), y fue agregada solución 4N de hidróxido de sodio en agua (1.2 ml). La mezcla fue agitada a temperatura ambiente durante 4 h. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo obtenido fue disuelto en agua. La capa acuosa fue lavada con éter dietílico, acidificada con ácido clorhídrico 2N bajo un baño de hielo, y extraída con acetato de etilo. La capa del acetato de etilo fue lavada con agua y solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. Fue agregado éter dietílico:n-hexano (1:1) al residuo obtenido y el sólido precipitado fue separado por filtración y secado para producir el compuesto del título como un sólido blanco (600 mg).

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Ejemplo 114

Producción de ácido 3-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoico

1-[5-Ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-3-(2-trifluorometilfenil)pirrolidina (195 mg) producida por un método similar al del ejemplo 1 y 3-yodobenzoato de etilo (142 mg) fueron disueltos en 1,4-dioxano (1 ml) y ter-butanol (1 ml), y fueron agregados tris(dibencilideneacetona)dipaladio (14.2 mg), 2-diciclohexilfosfino-2'-(N,N-dimetilamino)bifenilo (24.3 mg) y carbonato de cesio (235 mg). La mezcla fue agitada toda la noche y calentada bajo reflujo. Después de permitir enfriar, el material insoluble fue filtrado a través de celite, y el filtrado fue concentrado bajo presión reducida. Fue agregada una solución saturada de carbonato ácido de sodio en agua al residuo obtenido, y la mezcla fue extraída con acetato de etilo. La capa de éter etílico fue lavada con solución salina, fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:acetona=1:1) para dar 3-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)-pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoato de etilo como un sólido amorfo blanco (179 mg).

Fue disuelto 3-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoato de etilo (179 mg) producido en la etapa anterior en tetrahidrofurano (1 ml) y etanol (1 ml), y fue agregada una solución 4N de hidróxido de sodio en agua (1 ml). La mezcla fue calentada bajo reflujo durante 2 h. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo obtenido fue disuelto en agua, y fue acidificado con ácido clorhídrico 2N bajo un baño de hielo. El sólido precipitado fue recolectado por filtración, fue lavado con agua y secado bajo

presión reducida para producir el compuesto del titulo como un sólido blanco (165 mg).

Ejemplo 115

Producción de ácido 5-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)-pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiofen-2-carboxílico

Fueron disueltos 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-3-(2-trifluorometilfenil)pirrolidina (220 mg) producido por un método similar al del ejemplo 1 y 5-bromotiofen-2-carboxilato de etilo (137 mg) en tolueno (4 ml), y fueron agregados acetato de paladio (13 mg), 2.2'-bis(difenilfosfino)-1.1'-binaftilo (36 mg) y carbonato de cesio (265 mg). La mezcla fue calentada bajo reflujo durante 6 h. Después de permitir enfriar, el material insoluble fue filtrado a través de celite, y el filtrado fue concentrado bajo presión reducida. Fue agregada una solución saturada de carbonato ácido de sodio en água al residuo obtenido, y la mezcla fue extraída con acetato de etilo. La capa de éter etílico fue lavada con solución salina, fue secada sobre el sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:acetona=1:1) para dar 5-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)-pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiofen-2-carboxilato de etilo (162 mg) como un sólido amorfo blanco.

Fue disuelto 5-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiofen-2-carboxilato de etilo (162 mg) producido en la etapa anterior en tetrahidrofurano (1 ml) y etanol (1 ml), y fue agregada una solución 4N de hidróxido de sodio en agua (1 ml). La mezcla fue calentada bajo reflujo

durante 3 h. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo obtenido fue disuelto en agua, y acidificado con 2N ácido clorhídrico bajo un baño de hielo. El sólido precipitado fue recolectado por filtración, fue lavado con agua y fue secado bajo presión reducida. El sólido obtenido fue purificado por cromatografía de gel de sílice (cloroformo:acetona=6:1), y recristalizado del acetato de etilo para producir el compuesto de título como sólido verde pálido (28 mg).

Ejemplo 116

Producción de ácido 2-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)-pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiazol-4-carboxílico

Etapa 1

Producción de 4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-tiocarboxamida

Fue disuelto 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-3-(2-trifluorometilfenil)pirrolidina (420 mg) producido por un método similar al del ejemplo 1 en cloroformo (10 ml), y fueron agregados trietilamina (0.139 ml) y 9-fluorenilmetoxicarbonilisotiocianato (285 mg) a temperatura ambiente. La mezcla fue agitada por 1 h. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=50:1). El producto purificado obtenido fue disuelto en N,N-dimetilformamida (7 ml), y piperidina (0.7 ml) fue agregado a temperatura ambiente. La mezcla fue agitada por 1 h y fue concentrada bajo presión reducida. El residuo fue disuelto en acetato de etilo, y la mezcla fue lavada con agua y solución salina, fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. Fue

agregado éter dietílico al residuo obtenido, y el sólido precipitado fue separado por filtración, fue lavado con agua y fue secado bajo presión reducida para producir el compuesto del título como un sólido blanco (287 mg).

Etapa 2

Producción de ácido 2-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)-pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiazol-4-carboxílico

Fue suspendido 4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)-pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-tiocarboxamida (280 mg) producido en la etapa anterior en etanol (5 ml), y fue agregado bromopiruvato de etilo (0.09 ml) a la suspensión obtenida. La mezcla fue calentada a reflujo durante 2 h. La mezcla de reacción fue concentrada bajo presión reducida, fue agregada agua al residuo obtenido, y la mezcla fue extraída con cloroformo. La capa del cloroformo fue lavada con solución saturada de carbonato ácido de sodio en agua y solución salina, fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=20:1) para dar 2-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiazol-4-carboxilato de etilo (361 mg) como un sólido amorfo blanco.

Fue disuelto 2-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiazol-4-carboxilato de etilo (355 mg) producido en la etapa anterior en tetrahidrofurano (0.6 ml) y metanol (0.3 ml), y solución 4N de hidróxido de sodio en agua (0.57 ml) fue agregado a temperatura ambiente. La mezcla fue agitada por 3 h. La mezcla de reacción fue concentrada bajo presión reducida, y fue agregada una solución 1N de hidróxido de sodio en agua al residuo obtenido, y la mezcla fue lavada con éter dietílico. La capa acuosa fue acidificada con

Ejemplo 117

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(5-metil-4H-[1.2.4]-triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Etapa 1

Producción de yodohidrato del 4-{5-ciclopropil-4-[(S)-3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-imidotiocarboxilato de metilo

Fue disuelto 4-{5-ciclopropil-4-[(S)-3-(2-trifluorometilfenil)-pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-tiocarboxamida (500 mg) producido por un método similar al del ejemplo 116, etapa 1 en cloroformo (5 ml), y fue agregado yoduro de metilo (0.1 ml). La mezcla fue agitada toda la noche a temperatura ambiente. La mezcla fue concentrada bajo presión reducida, fue agregado éter dietílico al residuo obtenido, y el sólido precipitado fue separado por filtración y secado para producir el compuesto del título como un sólido amarillo pálido (654 mg).

Etapa 2

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(5-metil-4H-[1.2.4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fueron suspendidos yodohidrato del 4-{5-ciclopropil-4-[(S)-3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-imidotiocarboxilato de metilo (317 mg) producido en la etapa anterior, hidrazida del ácido acético (50 mg) y acetato de sodio (43 mg) en dioxano (2 ml) y agua (0.4 ml), y la mezcla fue agitada toda la noche y calentada bajo reflujo. El solvente fue separado bajo presión reducida, fue agregada agua al residuo obtenido, y la mezcla fue extraída con acetato

de etilo. La capa del acetato de etilo fue lavada con solución salina y fue secada sobre sulfato de magnesio anhidro. La mezcla fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=10:1). El sólido amorfo obtenido fue disuelto en acetato de etilo (1 ml), y fue agregada una solución 4N de ácido clorhídrico en acetato de etilo (0.4 ml). El sólido precipitado fue separado por filtración y fue secado para producir el compuesto del título como cristales blancos (72 mg).

Ejemplo 118

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(5-ciclopropil-4H-[1.2.4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 117, el compuesto del título fue obtenido como cristales (253 mg) del yodohidrato del 4-{5-ciclopropil-4-[(S)-3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-imidotiocarboxilato de metilo (475 mg).

Ejemplo 119

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(5-hidroximetil-4H-[1.2.4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina.

Por un método similar al del ejemplo 117, el compuesto del título fue obtenido como cristales (25 mg) del yodohidrato del 4-{5-ciclopropil-4-[(S)-3-(2-

trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-imido-tiocarboxilato de metilo (317 mg).

Ejemplo 120

Producción de clorhidrato de 1-{5-ciclopropil-1-[1-(5-trifluorometil-4H-[1.2.4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 117, el compuesto del título fue obtenido como cristales blancos (130 mg) del yodohidrato del 4-{5-ciclopropil-4-[(S)-3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}-piperidin-1-imidotiocarboxilato de metilo (317 mg).

Ejemplo 121

Producción de 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(R)-3-(2-trifluorometilfenil)]pirrolidina

Etapa 1

Producción de 5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carboxilato de metilo

Fue disuelto 1-(1-benciloxicarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carboxilato de metilo (15.9 g) producido en el ejemplo 1, etapa 2 en metanol (12 ml), y fue agregado carbono de paladio (1.5 g). La mezcla fue agitada toda la noche bajo una atmósfera de hidrógeno. El catalizador fue filtrado, y el filtrado fue concentrado bajo presión reducida. Fue agregado n-hexano al residuo obtenido, y la filtración produjo el compuesto del título como un sólido amorfo blanco (9.66 g).

Etapa 2

Producción de 5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carboxilato de metilo.

Fue disuelto 5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carboxilato de metilo (2.82 g) producido en la etapa anterior en cloroformo (28 ml) y fue agregado trietilamina (1.58 ml).

Fue agregado 2-fluorofenilisocianato (1.4 ml) a la mezcla obtenida bajo un baño de hielo y la mezcla fue agitada a temperatura ambiente durante 1 h. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:acetato de etilo=2:3) para producir el compuesto del título como un sólido amorfo blanco (4.23 g).

Etapa 3

Producción de ácido 5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carboxílico.

Fue disuelto 5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carboxilato de metilo (4.23 g) producido en la etapa anterior en tetrahidrofurano (11 ml) y metanol (5 ml), y fue agregada una solución 4N de hidróxido de sodio en agua (11 ml). La mezcla fue agitada a 60°C durante 6 h. A la mezcla de reacción fue dejada enfriar y fue concentrada bajo presión reducida. El residuo obtenido fue disuelto en agua. La capa acuosa fue lavada con éter dietílico, y acidificada con ácido clorhídrico concentrado bajo un baño de hielo. El sólido precipitado fue separado por filtración, fue lavado con agua y n-hexano, y fue secado bajo presión reducida para producir el compuesto del título como un sólido blanco (3.89 g).

Etapa 4

Producción de 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-{(R)-3-(2-trifluorometilfenil)}pirrolidina.

Fueron disueltos ácido 5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carboxílico (101 mg) producido en la etapa anterior, 1-hidroxibenzotriazol (46 mg) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida (57 mg) en N,N-dimetilformamida (15 ml). Fueron agregados (R)-3-(2-trifluorometilfenil)pirrolidina (65 mg)* y 4-dimetilaminopiridina (37 mg) a la solución obtenida y la mezcla fue agitada toda la noche a temperatura ambiente. Fue agregada agua a la mezcla de reacción, y la mezcla fue extraída con acetato de etilo. La capa del acetato de etilo fue lavada con una solución saturada de carbonato ácido de sodio en agua y solución salina, secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por

cromatografía de gel de sílice (cloroformo:metanol=20:1) para producir el compuesto del título como un sólido amorfo blanco (136 mg).

$[\alpha]^{25}D$=+10.9 (c=0.495; EtOH).

*(R)-3-(2-Trifluorometilfenil)pirrolidina fue producida por un método similar al método del ejemplo 2, etapa 1 a la etapa 4 y usando (R)-4-isopropil-5.5-difeniloxazolidin-2-ona. $[\alpha]^{25}D$=-21.0 (c=0.500; EtOH).

Ejemplo 122

Producción de 1-{5-ciclopropil-1-[1-(1-metilciclopropilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(R)-3-(2-trifluorometilfenil)]pirrolidina

Etapa 1

Producción de 5-ciclopropil-1-[1-(1-metilciclopropilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carboxilato de metilo.

Fueron disueltos ácido 1-metilciclopropano-1-carboxílico (1.81 g), azida de difenilfosforilo (4.67 ml) y trietilamina (2.77 ml) en tolueno (30 ml), y la mezcla fue calentada bajo reflujo durante 1 h para producir el isocianato.

Fueron disueltos 5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carboxilato de metilo (1.50 g) producido en el ejemplo 121, etapa 1 y trietilamina (0.84 ml) en tetrahidrofurano (15 ml) y fue agregada una solución de isocianato en tolueno preparada de antemano hasta que el material de comienzo, (1-(piperidin-4-il)-5-ciclopropil-1H-pirazol-4-carboxilato de metilo), desaparezca. La mezcla de reacción fue concentrada bajo presión reducida, fue agregada agua al residuo obtenido, y la mezcla fue extraída con cloroformo. La capa de cloroformo fue lavada con una solución saturada de carbonato ácido de sodio en agua y solución salina, y fue

secada sobre sulfato de magnesio anhidro. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=15:1) para producir el compuesto del título como un sólido amorfo blanco (1.92 g).

Etapa 2

Producción de ácido 5-ciclopropil-1-[1-(1-metilciclopropil-carbamoil)piperidin-4-il]-1H-pirazol-4-carboxílico.

Fue disuelto 5-ciclopropil-1-[1-(1-metilciclopropilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carboxilato de metilo (1.92 g) producido en la etapa anterior en tetrahidrofurano (20 ml) y metanol (10 ml), y fue agregada una solución 4N de hidróxido de sodio en agua (15 ml). La mezcla fue agitada a 60°C durante 6 h. A la mezcla de reacción le fue dejado enfriar y fue concentrada bajo presión reducida. El residuo obtenido fue disuelto en agua y la capa acuosa fue lavada con éter dietílico. Bajo un baño de hielo, la mezcla fue acidificada con ácido clorhídrico concentrado y fue extraída con cloroformo. La capa de cloroformo fue lavada con solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El acetato de etilo fue agregado al residuo obtenido, y el sólido precipitado fue separado por filtración y fue secado para producir el compuesto del título como un sólido blanco (1.68 g).

Etapa 3

Producción de 1-{5-ciclopropil-1-[1-(1-metilciclopropilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(R)-3-(2-trifluorometilfenil)]pirrolidina

Fueron disueltos ácido 5-ciclopropil-1-[1-(1-metilciclopropil-carbamoil)piperidin-4-il]-1H-pirazol-4-carboxílico (91 mg) producido en la etapa anterior, 1-hidroxibenzotriazol (46 mg) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida (57 mg) en N,N-dimetilformamida (1.5 ml). Fueron agregados (R)-3-(2-

trifluorometilfenil)pirrolidina (65 mg) y 4-dimetilaminopiridina (37 mg) a la solución obtenida y la mezcla fue agitada toda la noche a temperatura ambiente. Fue agregada agua a la mezcla de reacción, y la mezcla fue extraída con acetato de etilo. La capa del acetato de etilo fue lavada con una solución saturada de carbonato ácido de sodio en agua y solución salina, secadas sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=15:1) para producir el compuesto del título como un sólido amorfo blanco (123 mg).

$[\alpha]^{25}D$=+13.1 (c=0.495; EtOH).

Ejemplo 123

Producción de 1-{5-ciclopropil-1-[1-(1-isopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(R)-3-(2-trifluorometilfenil)]pirrolidina

Etapa 1

Producción de 5-ciclopropil-1-[1-(1-isopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carboxilato de metilo

Fue disuelto 5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carboxilato de metilo (1.87 g) producido en el ejemplo 121, etapa 1 en cloroformo (20 ml), y fue agregada trietilamina (1.05 ml). Fue agregado isopropilisocianato (0.7 ml) a la mezcla obtenida bajo un baño de hielo y la mezcla fue agitada a temperatura ambiente durante 1 h. La mezcla de reacción fue concentrada bajo presión reducida, y el residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=15:1) para producir el compuesto del título como un sólido amorfo blanco (2.00 g).

Etapa 2

Producción de ácido 5-ciclopropil-1-[1-(1-isopropilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carboxílico

Fue disuelto 5-ciclopropil-1-[1-(1-isopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carboxilato de metilo (2.00 g) producido en la etapa anterior en tetrahidrofurano (6 ml) y metanol (3 ml), y fue agregada una solución 4N de hidróxido de sodio en agua (6 ml). La mezcla fue agitada a 60°C durante 4.5 h. A la mezcla de reacción le fue dejado enfriar y fue concentrada bajo presión reducida. El residuo obtenido fue disuelto en agua y la capa acuosa fue lavada con éter dietílico, y fue acidificada con ácido clorhídrico concentrado bajo un baño de hielo. La mezcla fue extraída con cloroformo. La capa del cloroformo fue lavada con solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida.

Fue agregado n-hexano al residuo obtenido, y el sólido precipitado fue separado por filtración y secado para producir el compuesto del título como un sólido blanco (1.58 g).

Etapa 3

Producción de 1-{5-ciclopropil-1-[1-(1-isopropilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(R)-3-(2-trifluorometilfenil)]pirrolidina

Fueron disueltos ácido 5-ciclopropil-1-[1-(1-isopropilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carboxílico (88 mg) producido en la etapa anterior, 1-hidroxibenzotriazol (46 mg) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida (57 mg) en N,N-dimetilformamida (1.5 ml). Fueron agregados (R)-3-(2-trifluorometilfenil)pirrolidina (65 mg) y 4-dimetilaminopiridina (37 mg) a la solución obtenida y la mezcla fue agitada toda la noche a temperatura ambiente. Fue agregada agua a la mezcla de reacción, y la mezcla fue extraída con acetato de etilo.

La capa de acetato de etilo fue lavada con solución saturada de carbonato ácido de sodio en agua y solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=15:1) para producir el compuesto del título como un sólido amorfo blanco (120 mg).

$[\alpha]^{25}D$=+14.2 (c=0.500; EtOH)

Ejemplo 124

Producción de 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 121, etapa 4, el compuesto del título fue obtenido como un sólido amorfo blanco (127 mg) del ácido 5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carboxílico (123 mg) y (S)-3-(2-trifluorometilfenil)pirrolidina (78 mg).

$[\alpha]^{25}D$=-10.8 (c=0.510; EtOH)

Ejemplo 125

Producción de 1-{5-ciclopropil-1-[1-(1-isopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 123, etapa 3, el compuesto del título fue obtenido como un sólido amorfo blanco (123 mg) del ácido 5-ciclopropil-1-[1-(1-isopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carboxílico (107 mg), (S)-3-(2-trifluorometilfenil)pirrolidina (79 mg).

$[\alpha]^{25}D$=-13.2 (c=0.515; EtOH)

Ejemplo 126

Producción de 1-{5-ciclopropil-1-[1-(1-metilciclopropilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Por un método similar al del ejemplo 122, etapa 3, el compuesto del título fue obtenido como un sólido amorfo blanco (149 mg) del ácido 5-ciclopropil-1-[1-(1-metilciclopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carboxílico (107 mg), (S)-3-(2-trifluorometilfenil)pirrolidina (76 mg).

$[\alpha]^{25}D$=-13.6 (c=0.500; EtOH)

Ejemplo 127

Producción de clorhidrato de (-)-3-(4-fluorofenil)-3-hidroximetil-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina

Etapa 1

Producción de ciano-(4-fluorofenil)acetato de etilo

Fue agregado tolueno (40 ml) a 4-fluorofenilacetonitrilo (15.0 g) y carbonato de dietilo (66.9 ml) y fue agregado etóxido de sodio (8.30 g). La mezcla fue agitada por 2 h mientras se evapora el solvente desde 110°C hasta 130°C. Después de permitir enfriar, la mezcla de reacción fue vertida en agua, y fue agregado ácido acético (13 ml). La mezcla fue agitada durante 5 min, y la mezcla fue extraída 3 veces con acetato de etilo. La capa orgánica fue lavada con agua y solución salina,

fue secada sobre sulfato de sodio anhidro y fue concentrada bajo presión reducida para producir el compuesto del título como un aceite amarillo pálido (25.0 g).

Etapa 2

Producción de 2-ciano-2-(4-fluorofenil)succinato de dietilo

Fue agregado tetrahidrofurano (40 ml) a hidruro de sodio al 60% (2.12 g), y fue agregada lentamente una solución de acetato de ciano-(4-fluorofenil)etilo (10.0 g) producido en la etapa anterior en tetrahidrofurano (40 ml) bajo un baño de hielo. La mezcla fue agitada por 40 min y fue agregado bromoacetato de etilo (6.4 ml) bajo un baño de hielo. La mezcla fue agitada a temperatura ambiente durante 3 hs. La mezcla de reacción fue concentrada bajo presión reducida, fue agregada agua al residuo, y la mezcla fue extraída 3 veces con acetato de etilo. La capa orgánica fue lavada con agua y solución salina, fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:acetato de etilo=5:1) para producir el compuesto del título como un aceite amarillo pálido (14.7 g).

Etapa 3

Producción de 3-(4-fluorofenil)-5-oxo-pirrolidin-3-carboxilato de etilo

Fue agregada una solución de 2-ciano-2-(4-fluorofenil)succinato de dietilo (7.0 g) producido en la etapa anterior en etanol (50 ml) a níquel Raney (7.0 g), y la mezcla fue agitada toda la noche bajo una atmósfera de hidrógeno. La mezcla de reacción fue filtrada a través de celite, y el filtrado y el lavado fueron combinados y concentrados bajo presión reducida. El residuo obtenido fue purificado por

cromatografía de gel de sílice (cloroformo:metanol=25:1) y un solvente mezcla de éter dietílico y n-hexano fue agregado al residuo sólido obtenido. La mezcla fue filtrada y secada para producir el compuesto del título como cristales blancos (3.96 g).

Etapa 4

Producción de 1-bencil-3-(4-fluorofenil)-5-oxo-pirrolidin-3-carboxilato de etilo

Fue agregado tetrahidrofurano (25 ml) a hidruro de sodio al 60% (1.63 g), y fue agregada lentamente una solución de 3-(4-fluorofenil)-5-oxo-pirrolidin-3-carboxilato de etilo (10.3 g) producido en la etapa anterior en tetrahidrofurano (30 ml)/N,N-dimetilformamida (10 ml) bajo un baño de hielo. La mezcla fue agitada por 10 min. Bajo un baño de hielo, fue agregado bromuro de bencilo (4.86 ml). La mezcla fue agitada a la misma temperatura durante 30 min y a temperatura ambiente durante 3.5 h. La mezcla de reacción fue concentrada bajo presión reducida, fue agregada agua al residuo, y la mezcla fue extraída 3 veces con acetato de etilo. La capa orgánica fue lavada con agua y solución salina, fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:acetato de etilo=2:1) para producir el compuesto del título como un aceite amarillo pálido (12.1 g).

Etapa 5

Producción de 1-bencil-3-(4-fluorofenil)-3-hidroximetilpirrolidina

Fue agregado tetrahidrofurano (20 ml) al hidruro de litio aluminio (1.16 g) y fue agregada lentamente una solución de 1-bencil-3-(4-fluorofenil)-5-oxo-pirrolidin-3-carboxilato de etilo (4.16 g) producido en la etapa anterior en tetrahidrofurano (20 ml) bajo un baño de hielo. La mezcla fue agitada bajo reflujo

durante 3.5 h. Después de permitir enfriar, fueron agregados agua (0.9 ml), solución 4N de hidróxido de sodio en agua (0.9 ml) y agua (2.7 ml) sucesivamente bajo un baño de hielo, y fueron agregados éter dietílico y sulfato de magnesio. La mezcla fue agitada por 20 min. y fue filtrada a través de Celite. El filtrado y el lavado fueron combinados y concentrados bajo presión reducida para producir el compuesto del título como un aceite amarillo pálido (3.18 g).

Etapa 6

Producción de 3-(4-fluorofenil)-3-hidroximetilpirrolidina

A una solución de 1-bencil-3-(4-fluorofenil)-3-hidroximetil-pirrolidina (3.18 g) producido en la etapa anterior en metanol (30 ml) fue agregado hidróxido de paladio (300 mg), y la mezcla fue agitada toda la noche bajo una atmósfera de hidrógeno (3 atm). La mezcla de reacción fue filtrada a través de Celite, y el filtrado y lavado fueron combinados y concentrados bajo presión reducida para producir el compuesto del título como un aceite amarillo pálido (2.30 g).

Etapa 7

Producción de 3-(4-fluorofenil)-3-hidroximetil-pirrolidin-1-carboxilato de ter-butilo

A 3-(4-fluorofenil)-3-hidroximetilpirrolidina (2.30 g) producido en la etapa anterior fue agregado tetrahidrofurano (40 ml) y trietilamina (5.7 ml), y fue agregado di-ter-butildicarbonato (4.60 g) bajo un baño de hielo. La mezcla fue agitada toda la noche a temperatura ambiente. La mezcla de reacción fue concentrada bajo presión reducida, y fue agregado acetato de etilo. La mezcla fue lavada con agua y solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:acetato de etilo=2:1) para producir el compuesto del título como un

aceite incoloro (2.70 g).

Etapa 8

Producción de (-)-3-(4-fluorofenil)-3-hidroximetilpirrolidina

Al 3-(4-fluorofenil)-3-hidroximetil-pirrolidin-1-carboxilato de ter-butilo (1.02 g) producido en la etapa anterior fue agregado cloroformo (10 ml), trietilamina (962 ml) y 4-dimetilaminopiridina (421 mg), y fue agregado cloruro de (S)-(+)-3.3.3-trifluoro-2-metoxi-2-fenilpropionilo (969 ml) bajo un baño de hielo. La mezcla fue agitada a temperatura ambiente durante 1 h. La mezcla de reacción fue concentrada bajo presión reducida, fue agregada agua al residuo, y la mezcla fue extraída 3 veces con acetato de etilo. La capa orgánica fue lavada con una solución acuosa de sulfato ácido de potasio, con agua, con una solución de carbonato ácido de sodio en agua y solución salina, fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:éter dietílico=5:3) para dar el diastereómero menos polar como un aceite incoloro (871 mg). Adicionalmene, el diastereómero más polar fue obtenido como un aceite incoloro (781 mg). El aceite incoloro (871 mg) del diastereómero menos polar fue disuelto en tetrahidrofurano (4 ml) y metanol (2 ml), y fue agregada solución 4N de hidróxido de sodio en agua (2.6 ml). La mezcla fue agitada a 60°C durante 40 min. La mezcla de reacción fue concentrada bajo presión reducida y fue agregada agua al residuo. La mezcla fue extraída 3 veces con éter dietílico. La capa orgánica fue lavada con solución salina, fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida para dar un aceite incoloro (481 mg). El metanol (3 ml) y una solución 4N de ácido clorhídrico en acetato de etilo (3.3 ml) fue agregado al aceite incoloro obtenido (481 mg) y la mezcla fue agitada toda la noche a temperatura ambiente. La mezcla de reacción fue concentrada bajo presión reducida

y fue agregada agua al residuo. La mezcla fue lavada con éter dietílico, y la capa acuosa fue alcalinizada con una solución 2N de hidróxido de sodio en agua. La mezcla fue extraída 5 veces con cloroformo. La capa orgánica fue lavada con solución salina, secada sobre sulfato de sodio anhidro, concentrada bajo presión reducida para producir el compuesto del título como un aceite incoloro (312 mg).

$[\alpha]^{25}D$=-9.70 (c=0.598; EtOH)

Producción de (+)-3-(4-fluorofenil)-3-hidroximetilpirrolidina

Por un método similar al de producción de (-)-3-(4-fluorofenil)-3-hidroximetilpirrolidina y usando el aceite incoloro (781 mg) del diastereómero más polar, el compuesto del título fue obtenido como un aceite incoloro (251 mg).

$[\alpha]^{25}D$=+10.37 (c=0.588; EtOH)

Etapa 9

Producción de 5-(1-metilciclopropil)-1-(1-pirimidin-2-il-piperidin-4-il)-1H-pirazol-4-carboxilato de ter-butilo

Fueron disueltos 5-(1-metilciclopropil)-1-(piperidin-4-il)-1H-pirazol-4-carboxilato de ter-butilo (1.15 g) producido por un método similar al del ejemplo 121, etapa 1 y 2-cloropirimidina (700 mg) en 1,4-dioxano (12 ml), y fueron agregados acetato de paladio (85 mg), 2.2'-bis(difenilfosfino)-1.1'-binaftilo (352 mg) y carbonato de cesio (1.84 g). La mezcla fue calentada bajo reflujo durante 3 h. Después de permitir enfriar, el material insoluble fue filtrado a través de celite, y el filtrado fue concentrado bajo presión reducida. Una solución saturada de carbonato ácido de sodio en agua fue agregada al residuo obtenido, y la mezcla fue extraída con acetato de etilo. La capa de éter etílico fue lavada con solución salina, fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:acetato de etilo

=2:1) para producir el compuesto del título como un sólido amorfo blanco (922 mg).

Etapa 10

Producción de clorhidrato de ácido 5-(1-metilciclopropil)-1-(1-pirimidin-2-il-piperidin-4-il)-1H-pirazol-4-carboxílico

Fue disuelto 5-(1-metilciclopropil)-1-(1-pirimidin-2-il-piperidin-4-il)-1H-pirazol-4-carboxilato de ter-butilo (922 mg) producido en la etapa anterior en cloroformo (2 ml), y fue agregado ácido trifluoracético (4 ml). La mezcla fue agitada toda la noche a temperatura ambiente. La mezcla de reacción fue concentrada bajo presión reducida, y el cristal obtenido fue disuelto en tetrahidrofurano. Fue agregada una solución 4N ácido clorhídrico en acetato de etilo (2 ml), y la mezcla fue concentrada bajo presión reducida. El residuo cristalino obtenido fue molido lavando con acetato de etilo (10 ml) durante 1 h para producir el compuesto del título como un sólido blanco (800 mg).

Etapa 11

Producción de clorhidrato de (-)-3-(4-fluorofenil)-3-hidroximetil-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina

Fueron disueltos clorhidrato de ácido 5-(1-metilciclopropil)-1-(1-pirimidin-2-il-piperidin-4-il)-1H-pirazol-4-carboxílico (150 mg) producido en la etapa anterior, 1-hidroxibenzotriazol (81 mg) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida (102 mg) en N,N-dimetilformamida (3 ml). (-)-3-(4-fluorofenil)-3-hidroximetilpirrolidina (88 mg) producido en la etapa 8, trietilamina (0.057 ml) y 4-dimetilaminopiridina (50 mg) fue agregado a la solución obtenida, y la mezcla fue agitada toda la noche a temperatura ambiente. Fue agregada agua a la mezcla de reacción, y la mezcla fue extraída con acetato de etilo. La capa del acetato de etilo fue lavada con una solución saturada de carbonato ácido de sodio en agua y solución

salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía de gel de sílice (cloroformo:metanol=20:1) y la base libre obtenida fue disuelta en metanol (3 ml). Fue agregada una solución 4N de ácido clorhídrico en 1,4-dioxano (0.2 ml), y la mezcla fue concentrada bajo presión reducida. El residuo cristalino obtenido fue pulverizado por lavado con acetato de etilo (3 ml) durante 15 min para producir el compuesto del título como cristales blancos (203 mg).

$[\alpha]^{25}D$=-21.3 (c=0.506; MeOH)

Ejemplo 128

Producción de clorhidrato de (+)-3-(4-fluorofenil)-3-hidroximetil-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina

Por un método similar al del ejemplo 127, etapa 11, el compuesto del título fue obtenido como cristales blancos (198 mg) del clorhidrato del ácido 5-(1-metilciclopropil)-1-(1-pirimidin-2-il-piperidin-4-il)-1H-pirazol-4-carboxílico (150 mg), (+)-3-(4-fluorofenil)-3-hidroximetilpirrolidina (88 mg) producido en el ejemplo 127, etapa 8.

$[\alpha]^{25}D$=+26.0 (c=0.508; MeOH)

Ejemplo 129

Producción de clorhidrato de 1-[5-ciclopropil-1-(1-pirazin-2-il-piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

El compuesto del título fue obtenido como un sólido amorfo amarillo (165 mg) del clorhidrato del ácido 1-[5-ciclopropil-1-(1-pirazin-2-il-piperidin-4-il)-1H-pirazol-4-carboxílico (281 mg) producido por un método similar al del ejemplo 127.

Ejemplo 130

Producción de 1-[1-(trans-4-carbamoilciclohexil)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Etapa 1

Producción de trans-4-(2-ter-butoxicarbonilhidrazino)-ciclohexancarboxilato de etilo

Fueron disueltos 4-ciclohexancarboxilato de etilo (8.0 g) y carbazato de ter-butilo (6.2 g) en cloroformo (150 ml), y fueron agregados ácido acético (5.4 ml) y triacetoxiborohidruro de sodio (30 g) bajo un baño de hielo. La mezcla fue devuelta gradualmente a temperatura ambiente, y la mezcla fue agitada por 7 h. La mezcla de reacción fue vertida en una solución saturada de carbonato ácido de sodio en agua, y la mezcla fue extraída con acetato de etilo. La capa orgánica fue lavada con agua y solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:acetato de etilo=4:1) para producir el compuesto del título como un sólido blanco (4.63 g).

Etapa 2

Producción de clorhidrato del trans-4-hidrazinciclohexan-carboxilato de etilo

Fue disuelto trans-4-(2-ter-butoxicarbonilhidrazino)ciclohexan-

carboxilato de etilo (4.63 g) producido en la etapa anterior en etanol (30 ml), y fue agregada una solución 4N de ácido clorhídrico en acetato de etilo (82 ml). La mezcla fue agitada por 5.5 h. La mezcla fue concentrada bajo presión reducida, y fue agregado éter dietílico al residuo obtenido. La mezcla fue filtrada y secada para producir el compuesto del título como un polvo blanco (3.86 g).

Etapa 3

Producción de 1-(trans-4-etoxicarbonilciclohexane)-5-ciclopropil-1H-pirazol-4-carboxilato de ter-butilo

Fueron disueltos clorhidrato del trans-4-hidrazin-ciclohexancarboxilato de etilo (3.80 g) obtenido en la etapa anterior y 2-ciclopropilcarbonil-3-dimetilaminoacrilato de ter-butilo (3.71 g) sintetizado por un método similar al del ejemplo 1, etapa 1 en etanol (50 ml), y fue agregado trietilamina (4.32 ml). La mezcla fue agitada bajo reflujo durante 1 h. Después de permitir enfriar, la mezcla fue concentrada bajo presión reducida, y fue agregada agua al residuo. La mezcla fue extraída 3 veces con acetato de etilo. La capa orgánica fue lavada con agua y solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (n-hexano:acetato de etilo=5:1) para producir el compuesto del título como un líquido amarillo (4.80 g).

Etapa 4

Producción de ácido 1-(trans-4-etoxicarbonilciclohexane)-5-ciclopropil-1H-pirazol-4-carboxílico

A una solución de 1-(trans-4-etoxicarbonilciclohexano)-5-ciclopropil-1H-pirazol-4-carboxilato de ter-butilo (4.80 g) obtenido en la etapa anterior en cloroformo (14 ml) le fue agregado ácido trifluoracético (14 ml), y la mezcla fue

calentada a 40°C y agitada durante 1.5 h. Después de permitir enfriar, la mezcla fue concentrada bajo presión reducida y azeotrópicamente con tolueno. Fue agregado acetato de etilo al residuo para permitir la precipitación de cristal. La mezcla fue concentrada bajo presión reducida, fue agregado n-hexano al residuo, y los cristales fueron separados por filtración y secados para producir el compuesto del título como un polvo blanco (3.09 g).

Etapa 5

Producción de 1-{5-ciclopropil-1-(trans-4-etoxicarbonilciclohexil)-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fueron disueltos ácido 1-(trans-4-etoxicarbonilciclohexano)-5-ciclopropil-1H-pirazol-4-carboxílico (1.50 g) producido en la etapa anterior y (S)-3-(2-trifluorometilfenil)pirrolidina (1.16 g) en N,N-dimetilformamida (15 ml), y fueron agregados 1-hidroxibenzotriazol (825 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida (1.03 g) y 4-dimetilaminopiridina (658 mg). La mezcla fue agitada a temperatura ambiente durante 14 hs. El acetato de etilo fue agregado a la mezcla de reacción y la mezcla fue lavada dos veces con agua. La capa orgánica fue lavada con ácido clorhídrico 1N, con agua, con una solución saturada de carbonato ácido de sodio en agua, con agua y solución salina, fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=20:1) para producir el compuesto del título como una sustancia amorfa castaña (2.34 g).

Etapa 6

Producción de 1-[1-(trans-4-carboxiciclohexil)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fue disuelto 1-{5-ciclopropil-1-(trans-4-etoxicarbonilciclohexil)-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina (2.34 g) producido en la etapa anterior en tetrahidrofurano (12 ml) y metanol (6 ml), y fue agregada una solución de hidróxido de litio monohidrato (973 mg) en agua (12 ml). La mezcla fue agitada a 45°C durante 1 h. La mezcla fue concentrada bajo presión reducida, y fue agregada agua al residuo obtenido. La mezcla fue lavada dos veces con éter dietílico, y la capa acuosa fue acidificada con ácido clorhídrico 2N y fue extraída 3 veces con acetato de etilo. La capa orgánica fue lavada con agua y solución salina, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. Fueron agregados acetato de etilo y n-hexano al residuo obtenido, y el sólido precipitado fue separado por filtración y secado para producir el compuesto del título como un sólido blanco lechoso (2.13 g).

Etapa 7

Producción de 1-[1-(trans-4-carbamoilciclohexil)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fue disuelto 1-[1-(trans-4-carboxiciclohexil)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (300 mg) producido en la etapa anterior en N,N-dimetilformamida (3.5 ml), y fueron agregados 1-hidroxibenzotriazol (106 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida (133 mg), cloruro de amonio (80 mg) y trietilamina (0.105 ml). La mezcla fue agitada a temperatura ambiente durante 15 h. El acetato de etilo fue agregado a la mezcla de reacción, y la mezcla fue lavada consecutivamente con agua, con ácido clorhídrico 1N, con agua, con una solución saturada de carbonato ácido de sodio en agua, con agua y con

solución salina, secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. Fue agregado éter dietílico al residuo sólido obtenido y la mezcla fue agitada por 10 min. El sólido fue separado por filtración y secado para producir el compuesto del título como un sólido amorfo blanco (171 mg).

Ejemplo 131

Producción de 1-[5-ciclopropil-1-(trans-4-ureidociclohexil)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fue agregado tolueno (3.0 ml) a 1-[1-(trans-4-carboxiciclohexil)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (200 mg) producido en el ejemplo 130, etapa 6, y fueron agregados trietilamina (76 ml) y azida de difenilfosfónico (118 ml) bajo una atmósfera de argón. La mezcla fue calentada bajo reflujo durante 2 h. Después de permitir enfriar, la solución del tolueno fue agregada lentamente a una solución de amoníaco en agua al 28% (10 ml) y acetato de etilo (4 ml) bajo un baño de hielo, y la mezcla fue agitada a la misma temperatura durante 30 min. Fue agregada agua a la mezcla de reacción, y la mezcla fue extraída 3 veces con cloroformo. La capa orgánica fue lavada con agua y solución salina, fue secada sobre sulfato de sodio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía de gel de sílice (cloroformo:metanol=10:1). Fue agregado éter dietílico al residuo sólido obtenido y la mezcla fue agitada por 10 min. El sólido fue separado por filtración y secado para producir el compuesto del título como un sólido amorfo blanco (135 mg).

Ejemplo 132

Producción de 1-{5-ciclopropil-1-[trans-4-(1H-tetrazol-5-il)ciclohexil]-1H-pirazol-

4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Etapa 1

Producción de 1-[1-(trans-4-cianociclohexil)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fue disuelta 1-[1-(trans-4-carbamoilciclohexil)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (514 mg) producida en el ejemplo 130, etapa 7 en tetrahidrofurano (6 ml), y fueron agregados piridina (180 µl) y anhídrido del ácido trifluorometansulfónico (220 µl). La mezcla fue agitada a temperatura ambiente durante 1 h. Fue agregado adicionalmente piridina (180 µl) y anhídrido del ácido trifluorometansulfónico (220 µl), y la mezcla fue agitada a temperatura ambiente durante 1 h. La mezcla fue concentrada bajo presión reducida, y fue agregada una solución acuosa 1N de sulfato ácido de postasio. La mezcla fue extraída con acetato de etilo. La capa de acetato de etilo fue lavada con agua, fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía (cloroformo:metanol=15:1) para producir el compuesto del título como un sólido amorfo amarillo pálido (207 mg).

Etapa 2

Producción de 1-{5-ciclopropil-1-[trans-4-(1H-tetrazol-5-il)-ciclohexil]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina

Fue disuelto 1-[1-(trans-4-cianociclohexil)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina (207 mg) producida en la etapa anterior en 1,4-dioxano (2.5 ml), y fue agregado azidotributilestaño (188 mg). La

mezcla fue calentada toda la noche bajo reflujo. Fue agregado azidotributilestaño (94 mg) y la mezcla fue calentada bajo reflujo durante 4 h. La mezcla fue concentrada bajo presión reducida, fue agregado ácido clorhídrico 1N, y la mezcla fue extraída dos veces con cloroformo. La capa de cloroformo fue secada sobre sulfato de magnesio anhidro, y fue concentrada bajo presión reducida. El residuo obtenido fue purificado por cromatografía (cloroformo:metanol=25:2) y fue concentrada bajo presión reducida. Fue agregado éter diisopropílico al residuo obtenido, y el sólido precipitado fue recolectado por filtración, y fue secado para producir el compuesto del título como un sólido amorfo blanco (122 mg).

Ejemplo 133

Producción de 1-{5-(1-metilciclopropil)-1-[1-(4-trifluorometilfenil-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 3, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 134

Producción de 1-{1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-5-(1-metoxiciclopropil)-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 3, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 135

Producción de 1-{1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-5-(1-

metilciclopropil)-1H-pirazol-4-carbonil}-3-fenil-3-trifluorometil-pirrolidina

Por un método similar al del ejemplo 3, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 136

Producción de 3-(2-clorofenil)-1-{5-ciclopropil-1-[1-(2.4-difluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina

Por un método similar al del ejemplo 3, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 137

Producción de 3-(2-cloropiridin-3-il)-1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina

Por un método similar al del ejemplo 3, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 138

Producción de 1-{1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-5-(2.2.3.3-tetrametilciclopropil)-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 3, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 139

Producción de 1-{5-ciclohexil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 3, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 140

Producción de 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometoxifenil)pirrolidina

Por un método similar al del ejemplo 3, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 141

Producción de 1-{5-ciclopropil-1-[1-(4-trifluorometilfenilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 3, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 142

Producción de 1-(5-ciclopropil-1-{1-[((S)-1-carboxi-2-metilpropil)-metilcarbamoil]piperidin-4-il}-1H-pirazol-4-carbonil)-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 12, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 143

Producción de 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-metoxi-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 3, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 144

Producción de 1-{1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-5-(1-hidroximetilciclopropil)-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 3, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 145

Producción de 1-{5-ciclopropil-1-[1-(tiazol-2-ilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 146

Producción de 1-{1-[1-(isopropoxicarbamoil)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 147

Producción de 1-{5-ciclopropil-1-[1-(4-fluorobencilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 148

Producción de 1-{1-[1-(2.3-dihidroindol-1-carbonil)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

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Ejemplo 149

Producción de 1-{1-[1-(2.3-dihidro[1.4]oxazin-4-carbonil)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 150

Producción de 1-{5-ciclopropil-1-[1-(2.6-dichloropiridin-3-ilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 151

Producción de 1-{5-(1-metilciclopropil)-1-[1-(2,3,4,5-tetrahidrobenzo[b]-azepin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)-pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 152

Producción de 4-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoato de etilo

Por un método similar al del ejemplo 114, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 153

Producción de 1-[1-(1-benciloxicarbonil-piperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 1, etapa 4, el compuesto del título fue obtenido.

Ejemplo 154

Producción de 1-{1-[1-(3-carboxi-3-metil-butiril)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 155

Producción de 1-{5-ciclopropil-1-[1-(2-fenoxiacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 156

Producción de 1-{1-[1-(3-clorobenzoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 157

Producción de 1-{1-[1-(2-clorobenzoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 158

Producción de 1-[5-ciclopropil-1-(1-oxalilpiperidin-4-il)-1H-pirazol-4-carbonil]-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 65, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 159

Producción de 1-{1-[1-(4-clorobenzoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 160

Producción de 1-(5-ciclopropil-1-{1-[2-(4-fluorofenil)acetil]piperidin-4-il}-1H-pirazol-4-carbonil)-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 161

Producción de 1-{5-ciclopropil-1-[1-(3-trifluorometilbenzoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 162

Producción de 1-{5-ciclopropil-1-[1-(3-metoxibenzoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 64, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 163

Producción de clorhidrato de 1-{1-[1-(4-fluorobencil)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 94, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 164

Producción de 1-[1-(1-bencensulfonil-piperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 108, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 165

Producción de 1-{1-[1-(4-carbamoilfenil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 166

Producción de 1-{5-ciclopropil-1-[1-(4-hidroximetilfenil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 167

Producción de 1-{1-[1-(5-carbamoil-piridin-2-il)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 168

Producción de 1-{1-[1-(4-aminofenil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 169

Producción de 1-(5-ciclopropil-1-{1-[4-(2-oxooxazolidin-3-il)fenil]-piperidin-4-il}-1H-pirazol-4-carbonil)-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 170

Producción de 1-(5-ciclopropil-1-{1-[4-(3-metoxiureido)fenil]piperidin-4-il}-1H-pirazol-4-carbonil)-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 171

Producción de 1-{5-ciclopropil-1-[1-(4-metansulfonilaminofenil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 172

Producción de 1-[1-(1-etoxicarbamoilpiperidin-4-il)-5-(1-metilciclopropil)-1H-pirazol-4-carbonil]-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 10, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 173

Producción de 1-[1-(5-cloropiridin-2-il)azetidin-3-il]-5-ciclopropil-1H-pirazol-4-

carbonil]-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 174

Producción de 1-{1-[1-(5-cloro-piridin-2-il)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-metoximetil-3-fenilpirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 175

Producción de 1-{1-[1-(5-ciano-piridin-2-il)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 176

Producción de clorhidrato de 3-(2-acetoxietil)-3-(4-fluorofenil)-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 177

Producción de clorhidrato de {(3S*.4R*)-3-metil-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}-4-fenilpirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 178

Producción de 6-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)nicotinato de metilo

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

600

Ejemplo 179

Producción de 2-{1-[5-(1-metilciclopropil)-1-(1-pirimidin-2-il-piperidin-4-il)-1H-pirazol-4-carbonil]pirrolidin-3-il}benzoato de metilo

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 180

Producción de clorhidrato de 3-(2-hidroximetilfenil)-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 181

Producción de 1-[5-ciclopropil-1-(1-piridin-2-il-piperidin-4-il)-1H-pirazol-4-carbonil]-3-hidroxi-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

601

Ejemplo 182

Producción de 1-{1-[1-(4-acetilaminofenil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 114, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 183

Producción de 4-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)-3-fluorobenzoato de sodio

Por un método similar al del ejemplo 114, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 184

Producción de 3-(2-cianofenil)-1-{5-ciclopropil-1-[1-(2-fluorofenil-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina

Por un método similar al del ejemplo 121, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

602

Ejemplo 185

Producción de clorhidrato de 3-hidroximetil-1-{1-[1-(4-metoxipirimidin-2-il)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-fenilpirrolidina

Por un método similar al del ejemplo 127, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 186

Producción de clorhidrato de 3-(3.5-difluorofenil)-3-hidroximetil-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina

Por un método similar al del ejemplo 127, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 187

Producción de 1-{1-[1-(3-cloro-piridin-2-il)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina

Por un método similar al del ejemplo 113, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 188

Producción de 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(tiazol-2-il)pirrolidina

Por un método similar al del ejemplo 121, el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 189

Producción de ácido (S)-2-[(trans-4-{5-ciclopropil-4-[3-(2-trifluorometil-fenil)-pirrolidin-1-carbonil]-pirazol-1-il}-ciclohexancarbonil)-metil-amino]-3-metilbutírico

Por un método similar al del ejemplo 130. el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

Ejemplo 190

Producción de 1-{5-(1-metilciclopropil)-1-[trans-4-(2-fluorofenil-carbamoil)ciclohexil]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina

Por un método similar al del ejemplo 130. el compuesto del título fue obtenido del compuesto de comienzo correspondiente.

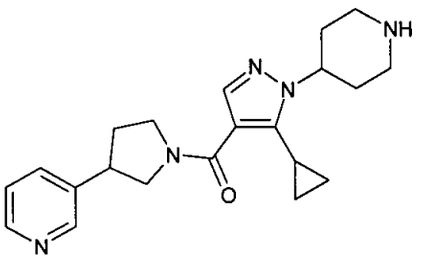
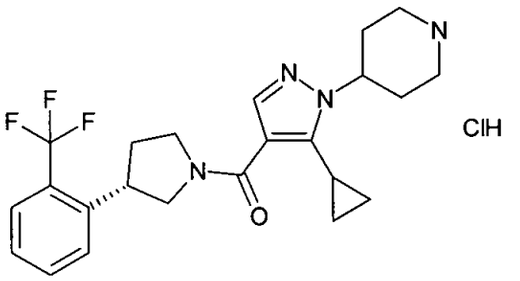
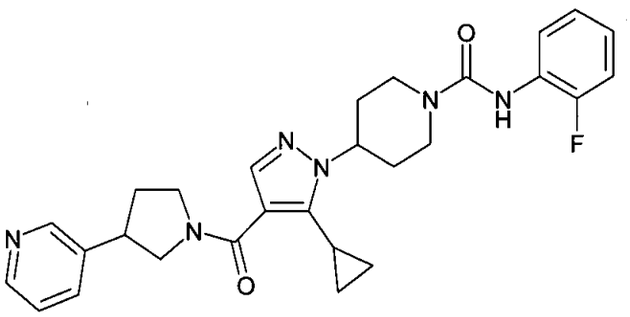
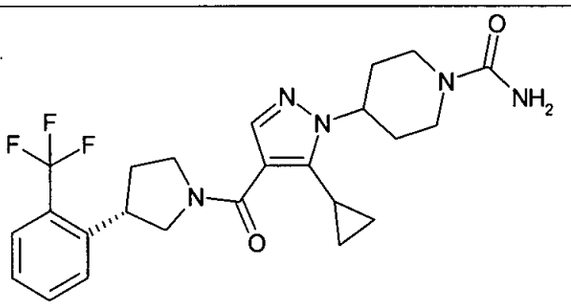
Ejemplo 191

Producción de ácido cis-4-{5-(1-metilciclopropil)-4-[3-(2-trifluorometilfenil)-pirrolidin-1-carbonil]-pirazol-1-il}-ciclohexancarboxílico

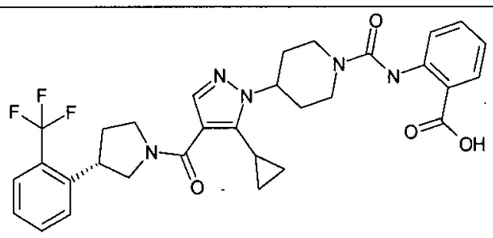
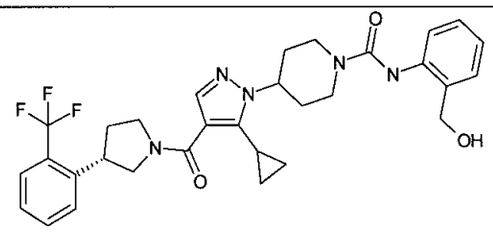
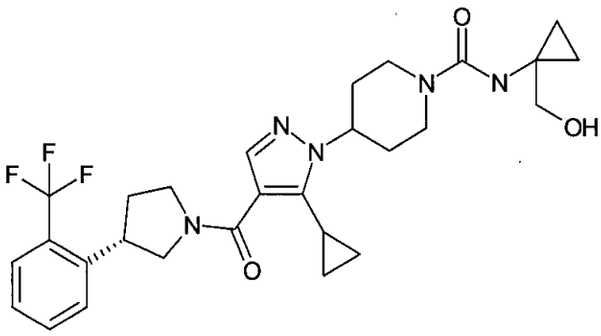
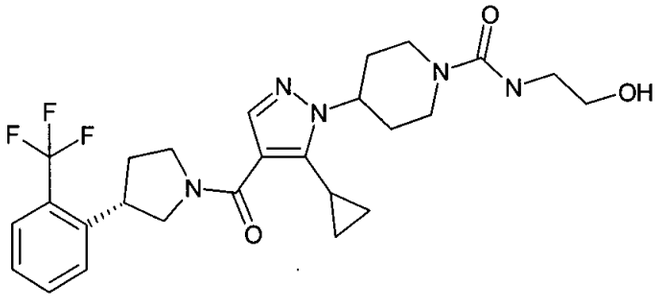
Por un método similar al del ejemplo 130, fue obtenido el compuesto del título desde el compuesto de comienzo correspondiente.

La fórmula estructural y los valores de las propiedades del compuesto de cada ejemplo se ilustran en el cuadro 1-1 hasta el cuadro 1-45.

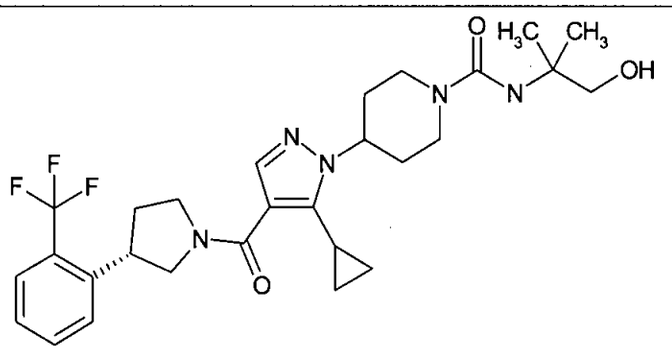
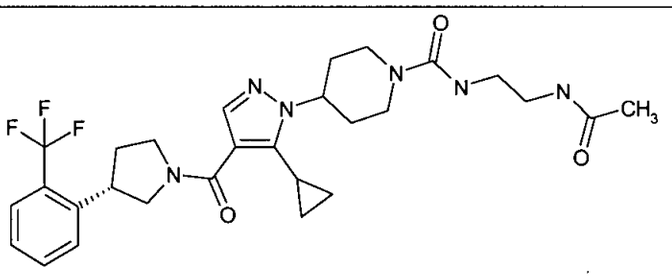
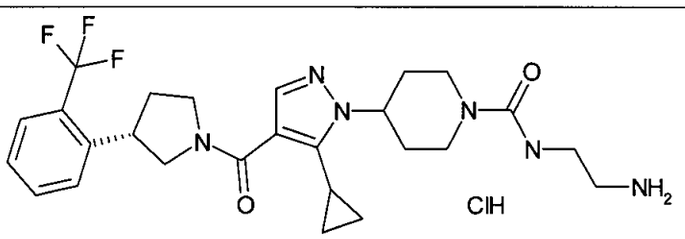
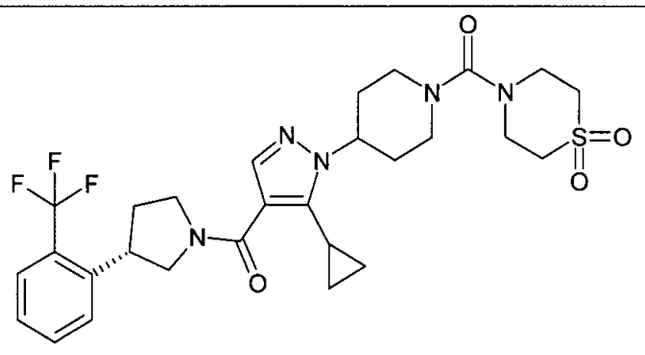
CUADRO 1-1

Ej. No.	Fórmula estructural	RMN
1		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.63-0.77 (2H; m); 0.97-1.11 (2H; m); 1.70-1.82 (1H; m); 1.96-2.67 (8H; m); 2.83-2.97 (2H; m); 3.33-3.53 (3H; m); 3.55-4.17 (3H; m); 4.50-4.64 (1H; m); 7.23-7.32 (1H; m); 7.48-7.64 (2H; m); 8.46-8.61 (2H; m)
2		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.59-0.75 (2H; m); 0.94-1.07 (2H; m); 1.86-2.36 (8H; m); 3.00-3.21 (2H; m); 3.30-3.93 (6H; m); 4.69-4.88 (1H; m); 7.44-7.64 (2H; m); 7.66-7.78 (3H; m); 8.83 (1H; brs); 9.22 (1H; brs)
3		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.65-0.83 (2H; m); 0.99-1.15 (2H; m); 1.73-1.84 (1H; m); 1.90-2.50 (6H; m); 3.02-3.20 (2H; m); 3.36-3.55 (1.5H; m); 3.56-3.80 (2H; m); 3.83-3.99 (1H; m); 4.06-4.17 (0.5H; m); 4.18-4.36 (2H; m); 4.54-4.71 (1H; m); 6.71 (1H; brs); 6.93-7.00 (1H; m); 7.02-7.14 (2H; m); 7.24-7.32 (1H; m); 7.50-7.62 (2H; m); 8.02-8.09 (1H; m); 8.47-8.59 (2H; m)
4		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.84 (2H; m); 1.03-1.14 (2H; m); 1.54-2.47 (7H; m); 2.94-3.14 (2H; m); 3.40-4.20 (7H; m); 4.47-4.67 (2H; m); 7.32-7.72 (6H; m)

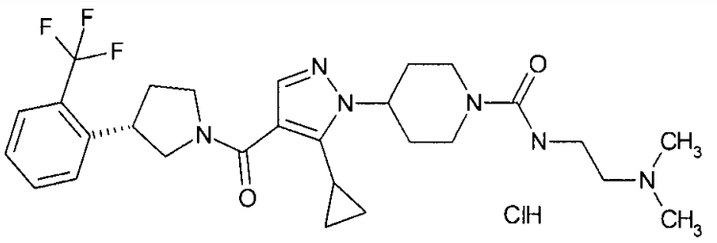
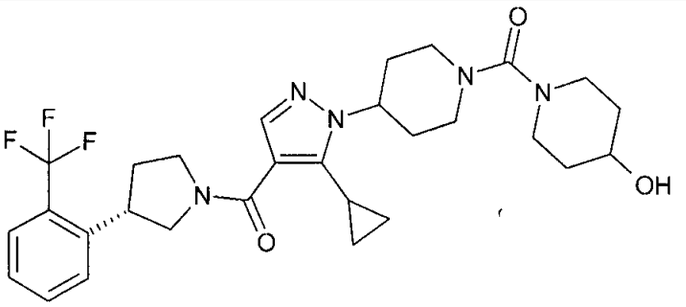
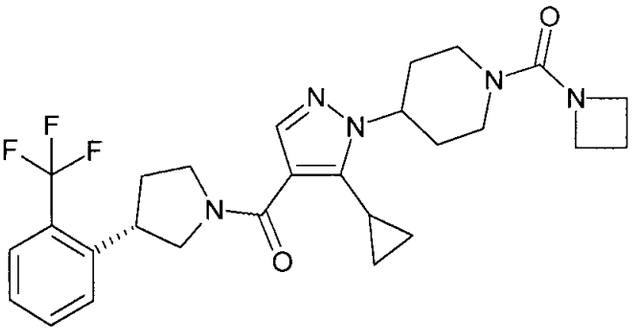
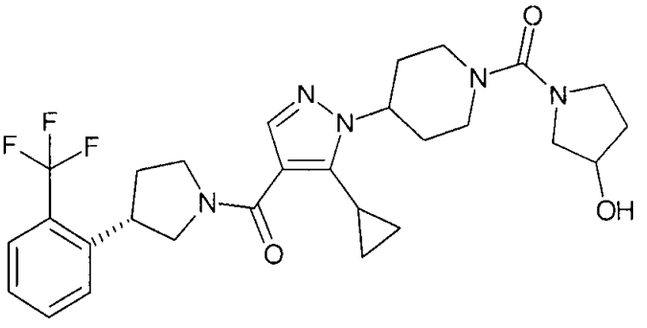
CUADRO 1-2

Ej. No.	Fórmula-estructural	RMN
5		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.60-0.75 (2H; m); 0.92-1.07 (2H; m); 1.81-2.36 (6H; m); 3.04-3.23 (2H; m); 3.44-3.93 (6H; m); 4.10-4.27 (2H; m); 4.65-4.83 (1H; m); 6.98-7.07 (1H; m); 7.39-7.61 (3H; m); 7.63-7.79 (3H; m); 7.92-8.02 (1H; m); 8.37-8.40 (1H; m); 11.0-11.2 (1H; m); 13.6 (1H; brs)
6		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.85 (2H; m); 1.01-1.14 (2H; m); 1.70-2.44 (7H; m); 2.72-2.86(1H; m); 2.97-3.13 (2H; m); 3.41-4.09 (5H; m); 4.20-4.35 (2H; m); 4.51-4.75 (3H; m); 6.97-7.04 (1H; m); 7.11-7.19 (1H; m); 7.28-7.60 (5H; m); 7.64-7.72 (1H; m); 7.92-7.98 (1H; m); 8.13-8.23 (1H; m)
7		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.61-0.94 (6H; m); 0.98-1.17 (2H; m); 1.64-1.86 (3H; m); 1.93-2.23 (3H; m); 2.24-2.48 (1H; m); 2.79-2.99 (2H; m); 3.32-4.22 (9H; m); 4.38-4.63 (1H; m); 5.64-5.87 (1H; m); 7.29-7.60 (4H; m); 7.60-7.71 (1H; m)
8		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.66-0.82 (2H;m); 0.99-1.12 (2H; m); 1.20-1.34 (1H; m); 1.67-1.88 (4H; m); 1.95-2.21 (3H;m); 2.23-2.46 (1H; m); 2.82-3.02 (2H; m); 3.28-3.48 (3H; m); 3.52-3.99 (5H; m); 3.99-4.22 (2H; m); 4.41-4.63 (1H; m); 5.16-5.33 (1H; m); 7.28-7.71 (5H; m)

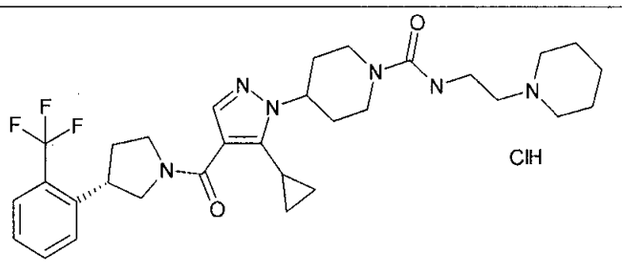
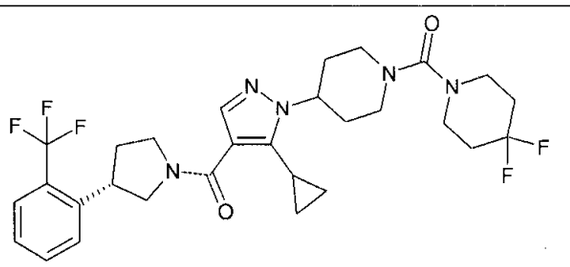
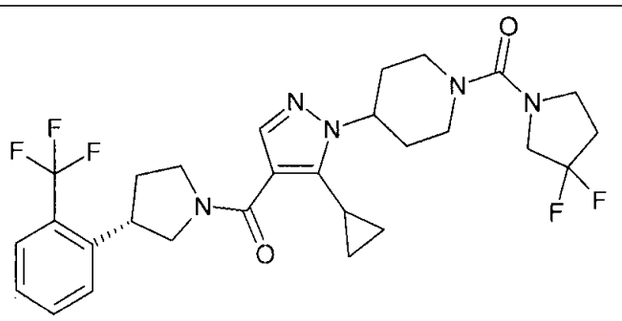
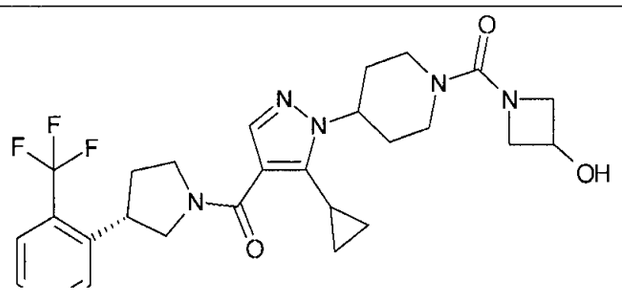
CUADRO 1-3

Ej. No.	Fórmula estructural	RMN
9		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.64-0.87 (2H; m); 0.98-1.17 (2H; m); 1.31 (3H; s); 1.32 (3H; s); 1.66-2.25 (6H; m); 2.26-2.47 (1H; m); 2.83-3.02 (2H; m); 3.39-4.20 (9H; m); 4.43-4.64 (1H; m); 4.67-4.84 (1H; m); 5.00-5.46 (1H; brs); 7.32-7.40 (1H; m); 7.41-7.60 (3H; m); 7.61-7.72 (1H; m)
10		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.67-0.82 (2H; m); 1.00-1.11 (2H; m); 1.70-1.83 (1H; m); 1.83-1.95 (3H; m); 1.99 (3H; br s); 2.04-2.22 (3H; m); 2.27-2.43 (1H; m); 2.86-3.01 (2H; m); 3.33-3.43 (4H; m); 3.54-4.18 (6H; m); 4.44-4.63 (1H; m); 5.42-5.53 (1H; m); 6.33-6.41 (1H; m); 7.32-7.71 (5H; m)
11		^{1}H-RMN (400MHz; DMSO-D6) δ: 0.58-0.74 (2H;m); 0.91-1.05 (2H; m); 1.78-2.34 (7H; m); 2.78-2.99 (5H; m); 3.22-3.94 (6H;m); 4.06-4.21 (2H; m); 4.54-4.72 (1H; m); 6.46-6.95 (1H;m); 7.42-7.77 (5H; m); 7.88-8.03 (3H; m)
12		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.86 (2H; m); 1.01-1.16 (2H; m); 1.71-1.86 (1H; m); 1.89-2.46 (6H; m); 2.91-3.15 (6H; m); 3.40-4.14 (11H; m); 4.47-4.67 (1H; m); 7.32-7.73 (5H; m)

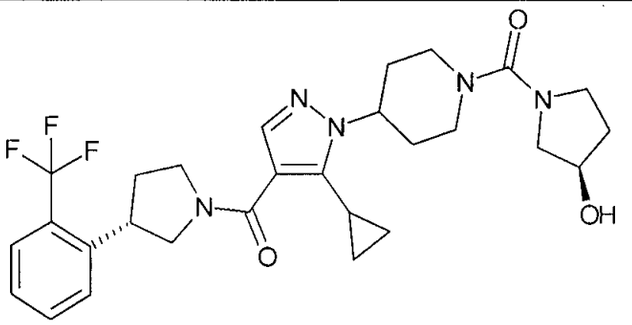
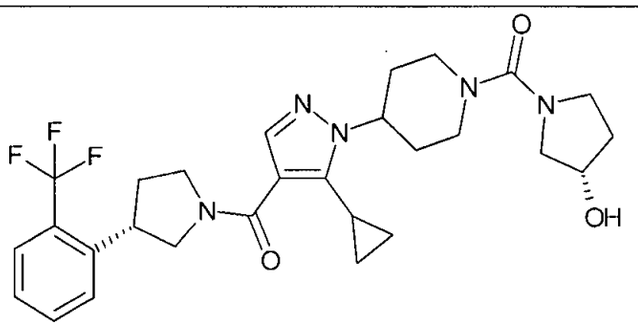
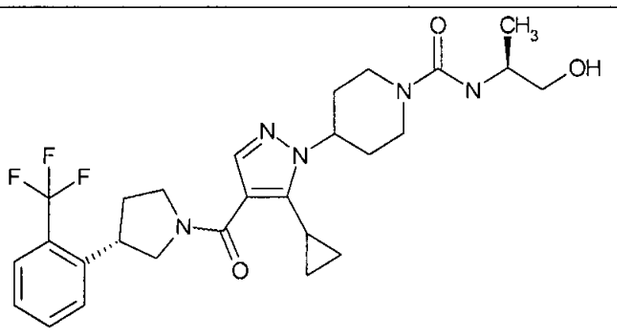
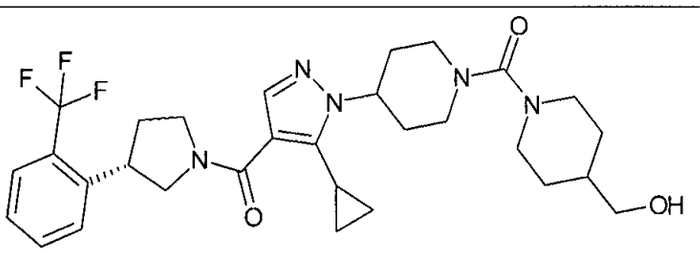
CUADRO 1-4

Ej. No.	Fórmula estructural	RMN
13		^{1}H-RMN (400MHz; DMSO-D6) δ: 0.68-0.86 (2H;m); 1.00-1.15 (2H; m); 1.58-2.49 (15H; m); 2.84-3.03 (2H; m); 3.20-3.39 (2H;m); 3.41-4.25 (7H; m); 4.44-4.65 (1H; m); 5.13-5.29 (1H; m); 7.31-7.73 (5H; m)
14		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.71-0.82 (2H; m); 1.03-1.12 (2H; m); 1.46-1.60 (3H; m); 1.72-1.97 (5H; m); 2.00-2.44 (4H; m); 2.80-3.07 (4H; m); 3.42-4.10 (10H; m); 4.43-4.61 (1H; m); 7.32-7.71 (5H; m)
15		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.83 (2H; m); 1.02-1.14 (2H; m); 1.71-2.45 (9H; m); 2.81-2.96 (2H; m); 3.42-4.22 (11H; m); 4.45-4.63 (1H; m); 7.32-7.72 (5H; m)
16		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.66-0.85 (2H; m); 0.99-1.17 (2H; m); 1.71-2.45 (10H; m); 2.79-3.00 (2H; m); 3.27-4.11 (11H; m); 4.39-4.63 (2H; m); 7.32-7.73 (5H; m)

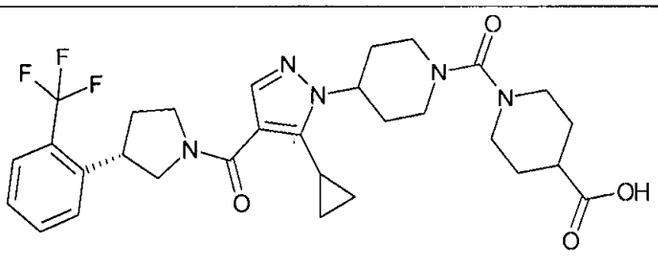
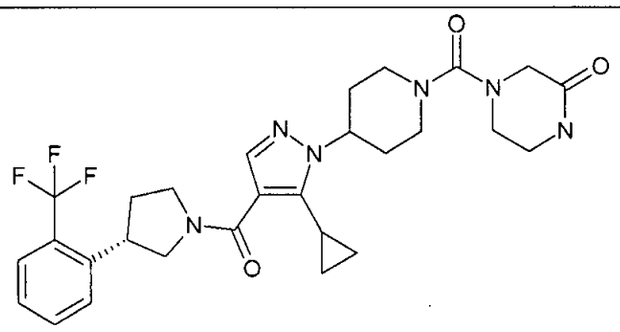
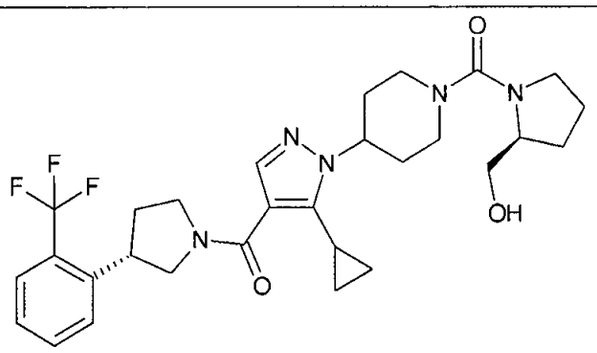
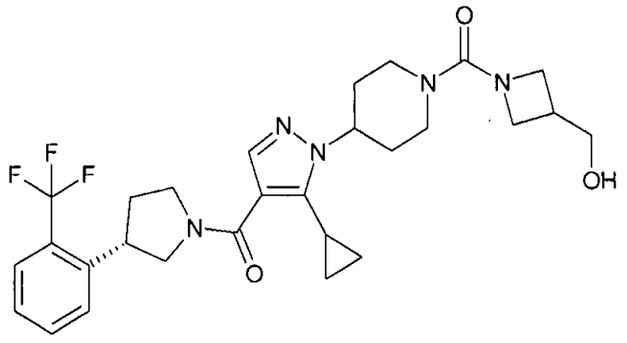
CUADRO 1-5

Ej. No.	Fórmula estructural	RMN
17		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.58-0.75 (2H; m); 0.92-1.06 (2H; m); 1.32-1.47 (1H; m); 1.63-1.98 (6H; m); 2.02-2.39 (2H;m); 2.78-3.00 (4H; m); 3.02-3.16 (2H; m); 3.38-3.54 (4H; m); 3.54-3.78 (3H; m); 3.80-4.55 (8H; m); 4.55-4.72 (1H; m); 7.01-7.20 (1H; brs); 7.41-7.60 (2H; m); 7.65-7.78 (3H; m); 9.99-10.16 (1H; brs)
18		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.86 (2H; m); 1.01-1.15 (2H; m); 1.71-2.45 (11H; m); 2.83-3.01 (2H; m); 3.33-3.51 (4H; m); 3.57-4.11 (7H; m); 4.45-4.62 (1H; m); 7.31-7.73 (5H; m)
19		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.86 (2H; m); 1.02-1.15 (2H; m); 1.70-2.46 (9H; m); 2.83-3.01 (2H; m); 3.41-4.12 (11H; m); 4.46-4.65 (1H; m); 7.31-7.73 (5H; m)
20		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.84 (2H; m); 1.00-1.16 (2H; m); 1.71-2.26 (6H; m); 2.27-2.45 (1H; m); 2.50-2.59 (1H; m); 2.81-3.00 (2H; m); 3.42-4.12 (9H; m); 4.46-4.68 (2H; m); 7.31-7.72 (5H; m)

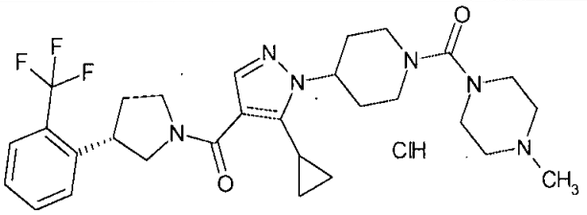
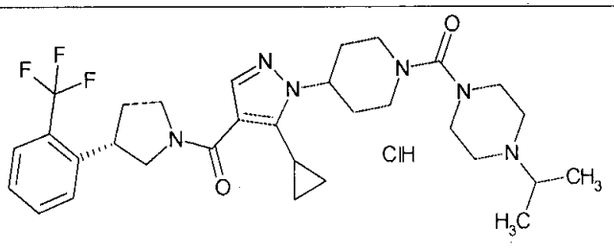
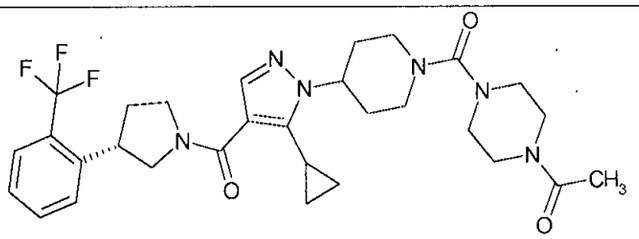
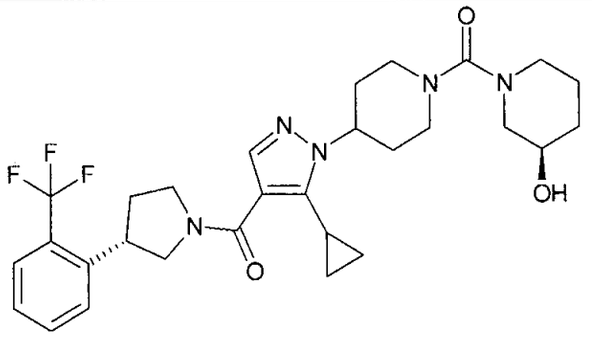
CUADRO 1-6

Ej. No.	Fórmula estructural	RMN
21		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.84 (2H; m); 0.99-1.15 (2H; m); 1.71-2.44 (10H; m); 2.78-2.99 (2H; m); 3.26-4.12 (11H; m); 4.42-4.62 (2H; m); 7.31-7.72 (5H; m)
22		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.85 (2H; m); 0.99-1.16 (2H; m); 1.68-2.47 (10H; m); 2.76-2.99 (2H; m); 3.27-4.11 (11H; m); 4.41-4.62 (2H; m); 7.32-7.73 (5H; m)
23		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.65-0.81 (2H;m); 1.05-1.15 (2H; m); 1.71-2.45 (7H; m); 1.94-2.44 (6H; m); 2.85-3.05 (2H; m); 3.35-4.20 (9H; m); 4.45-4.65 (1H; m); 4.65-4.75 (1H; m); 7.30-8.30 (5H; m)
24		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.67-0.83 (2H; m); 1.02-1.13 (2H; m); 1.15-1.32 (3H; m); 1.35-1.46 (1H; m); 1.63-2.45 (9H; m); 2.73-2.98 (4H; m); 3.40-4.12 (11H; m); 4.42-4.63 (1H; m); 7.29-7.74 (5H; m)

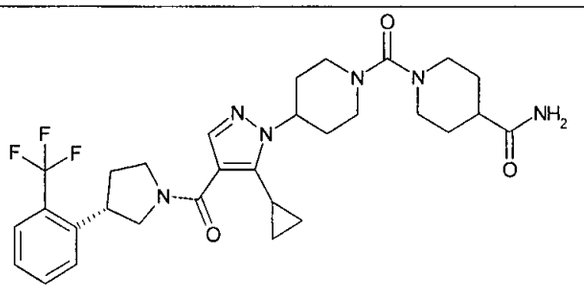
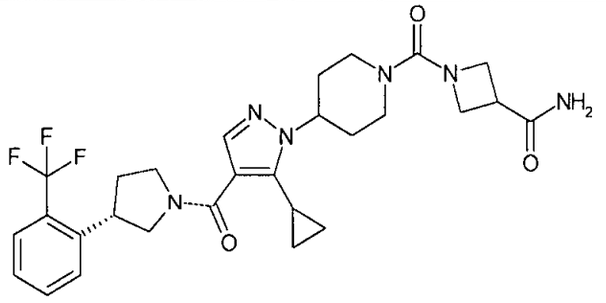
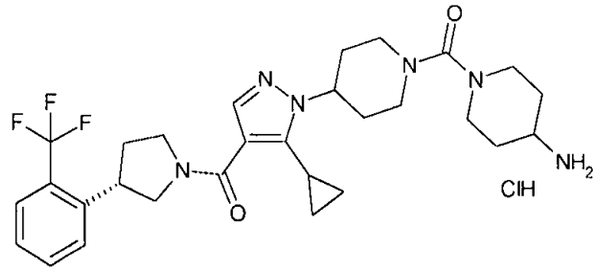
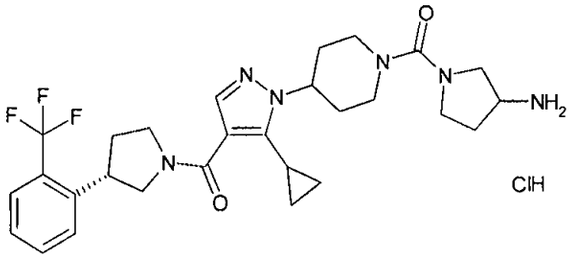
CUADRO 1-7

Ej. No.	Fórmula estructural	RMN
25		^{1}H-RMN (400MHz; DMSO-D6) δ: 0.59-0.74 (2H; m); 0.91-1.06 (2H; m); 1.42-1.63 (2H; m); 1.72-2.46 (10H; m); 2.75-3.03 (4H; m); 3.43-3.96 (9H; m); 4.48-4.72 (1H; m); 7.38-7.83 (5H; m); 12.1-12.4 (1H; m)
26		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.66-0.85 (2H; m); 0.97-1.17 (2H; m); 1.68-2.46 (7H; m); 2.84-3.08 (2H; m); 3.36-4.13 (13H; m); 4.44-4.67 (1H; m); 6.54-6.71 (1H; m); 7.30-7.73 (5H; m)
27		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.67-0.84 (2H; m); 1.00-1.15 (2H; m); 1.43-1.59 (1H; m); 1.61-2.45 (10H; m); 2.78-3.01 (2H; m); 3.32-4.10 (11H; m); 4.18-4.31 (1H; m); 4.45-4.63 (1H; m); 7.31-7.72 (5H; m)
28		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.64-0.83 (2H; m); 0.96-1.16 (2H; m); 1.70-2.29 (6H; m); 2.29-2.39 (1H; m); 2.67-2.69 (1H; m); 2.82-2.97 (2H; m); 3.38-4.18 (13H; m); 4.41-4.65 (1H; m); 7.30-7.74 (5H; m)

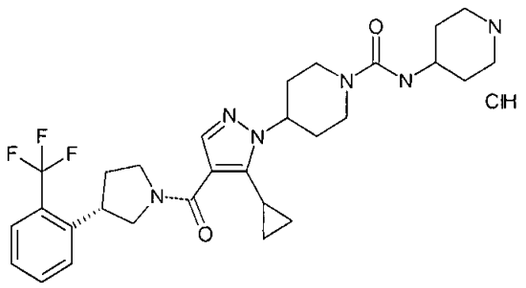
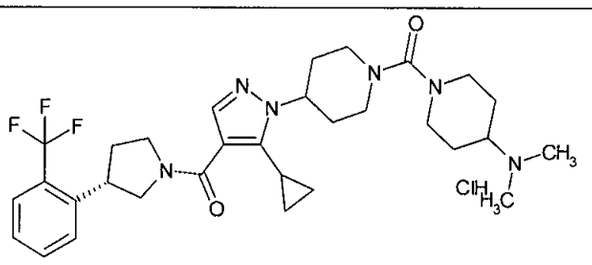
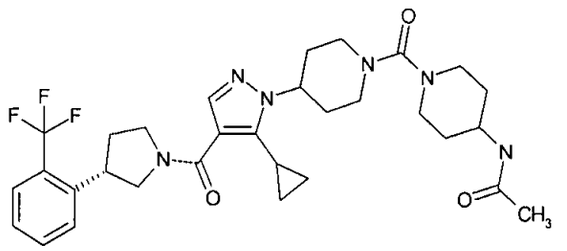
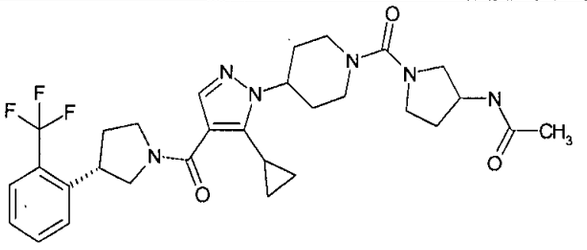
CUADRO 1-8

Ej. No.	Fórmula estructural	RMN
29		^{1}H-RMN (400MHz; DMSO-D6) δ: 0.59-0.73 (2H; m); 0.94-1.06 (2H; m); 1.79-2.34 (7H; m); 2.74-2.82 (3H; m); 2.89-3.93 (17H; m); 4.55-4.74 (1H; m); 7.42-7.80 (5H; m); 10.4-10.6 (1H; m)
30		^{1}H-RMN (400MHz; DMSO-D6) δ: 0.59-0.75 (2H; m); 0.92-1.06 (2H; m); 1.22-1.35 (6H; m); 1.77-2.46 (7H; m); 2.85-3.11 (5H; m); 3.21-3.96 (13H; m); 4.52-4.74 (1H; m); 7.42-7.82 (5H; m); 10.3-10.5 (1H; m)
31		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.85 (2H; m); 1.02-1.16 (2H; m); 1.71-2.47 (10H; m); 2.87-3.03 (2H; m); 3.20-4.15 (15H; m); 4.45-4.66 (1H; m); 7.31-7.73 (5H; m)
32		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.62-0.84 (2H; m); 0.97-1.15 (2H; m); 1.37-1.55 (1H; m); 1.55-1.96 (6H; m); 1.99-2.46 (5H; m); 2.77-3.03 (1H; m); 3.15-4.12 (12H; m); 4.38-4.65 (1H; m); 7.30-7.74 (5H; m)

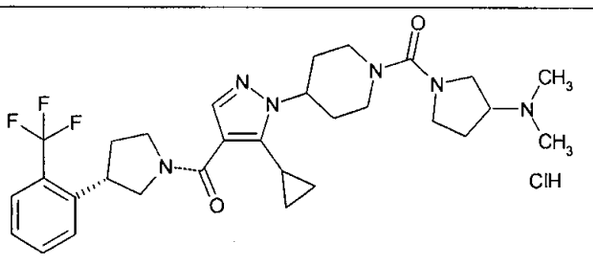
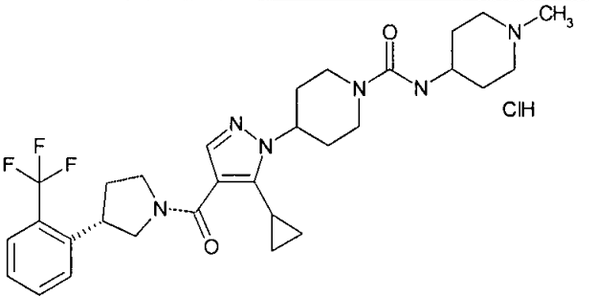
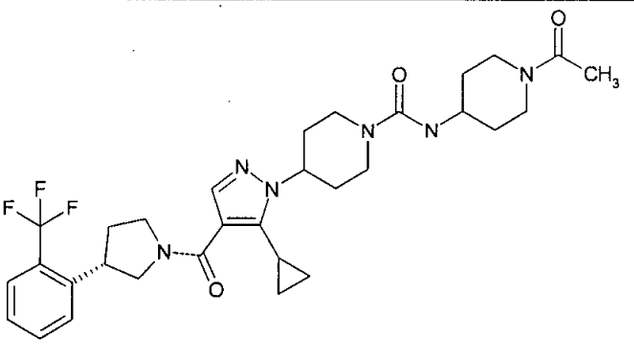
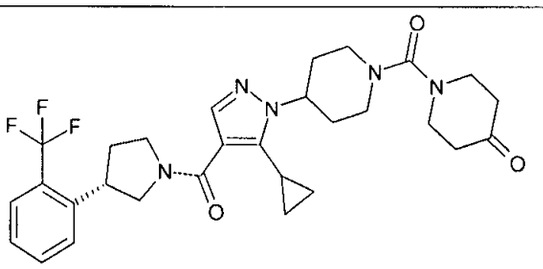
CUADRO 1-9

Ej. No.	Fórmula estructural	RMN
33		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.85 (2H; m); 1.01-1.14 (2H; m); 1.62-1.99 (7H; m); 1.99-2.47 (5H; m); 2.74-3.00 (4H; m); 3.41-3.53 (0.6H; m); 3.56-4.11 (8.4H; m); 4.43-4.61 (1H; m); 5.44 (1H; brs); 5.56 (1H; brs); 7.32-7.38 (1H; m); 7.39-7.60 (3H; m); 7.62-7.71 (1H; m)
34		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.83 (2H; m); 0.99-1.15 (2H; m); 1.67-1.96 (3H; m); 1.98-2.24 (3H; m); 2.25-2.44 (1H; m); 2.78-3.00 (2H; m); 3.20-3.39 (1H; m); 3.40-3.53 (0.5H; m); 3.53-4.09 (6.5H; m); 4.10-4.25 (4H; m); 4.40-4.66 (1H; m); 5.59 (1H; brs); 5.77 (1H; brs); 7.31-7.39 (1H; m); 7.40-7.60 (3H; m); 7.62-7.71 (1H; m)
35		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.59-0.72 (2H; m); 0.94-1.06 (2H; m); 1.39-1.56 (2H; m); 1.78-2.01 (6H; m); 2.05-2.34 (2H; m); 2.72-3.01 (4H; m); 3.24-3.27 (1H; m); 3.43-4.01 (9H; m); 4.53-4.70 (1H; m); 7.43-7.60 (2H; m); 7.66-7.77 (3H; m); 8.33 (3H; brs)
36		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.55-0.73 (2H; m); 0.89-1.08 (2H; m); 1.69-2.38 (10H; m); 2.77-3.02 (2H; m); 3.12-4.15 (11H; m); 4.52-4.73 (1H; m); 7.41-7.77 (3H; m); 8.18-8.40 (3H; m); 8.42-8.61 (1H; m); 9.36-

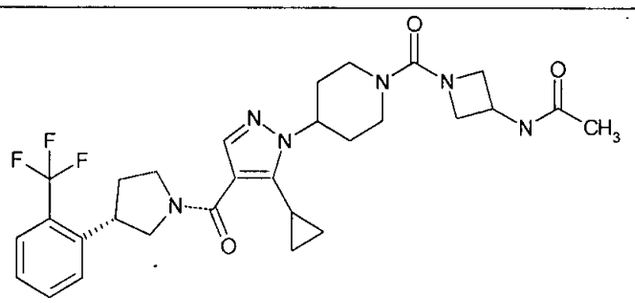
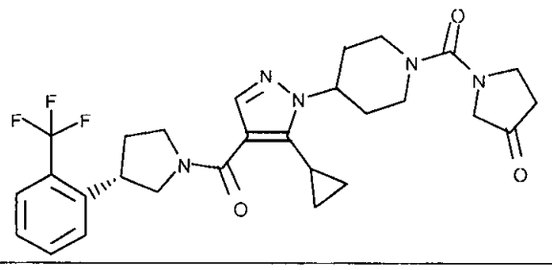
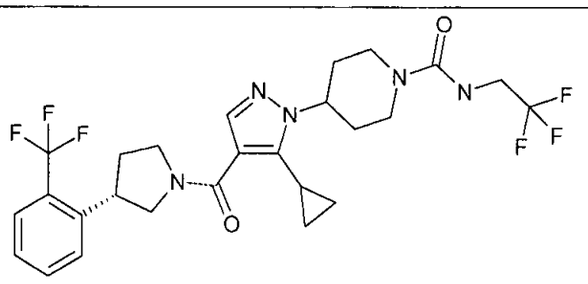
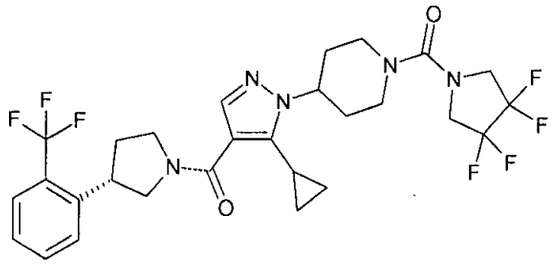
CUADRO 1-10

Ej. No.	Fórmula estructural	RMN
37		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.58-0.73 (2H; m); 0.92-1.04 (2H; m); 1.55-1.70 (2H; m); 1.74-1.98 (7H; m); 2.02-2.36 (2H; m); 2.73-3.02 (4H; m); 3.19-3.33 (2H; m); 3.45-4.32 (8H; m); 4.53-4.72 (1H; m); 6.44-6.62 (1H; m); 7.42-7.79 (5H; m); 8.62 (1H; br s); 8.72 (1H; br s)
38		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.58-0.74 (2H; m); 0.92-1.06 (2H; m); 1.47-1.68 (2H; m); 1.78-2.56 (8H; m); 2.62-3.03 (4H; m); 2.77 (6H; s); 3.24-3.94 (10H; m); 4.54-4.70 (1H; m); 7.42-7.62 (2H; m); 7.63-7.79 (3H; m); 10.2-10.4 (1H; m)
39		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.84 (2H; m); 1.02-1.14 (2H; m); 1.31-1.46 (2H; m); 1.71-2.45 (9H; m); 1.97 (3H; s); 2.81-3.00 (4H; m); 3.42-4.10 (10H; m); 4.44-4.61 (1H; m); 5.29-5.43 (1H; m); 7.33-7.72 (5H; m)
40		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.83 (2H; m); 1.00-1.13 (2H; m); 1.68-2.46 (13H; m); 2.81-3.00 (2H; m); 3.28-4.10 (10H; m); 4.36-4.63 (2H; m); 5.61-5.72 (1H; m); 7.31-7.70 (5H; m)

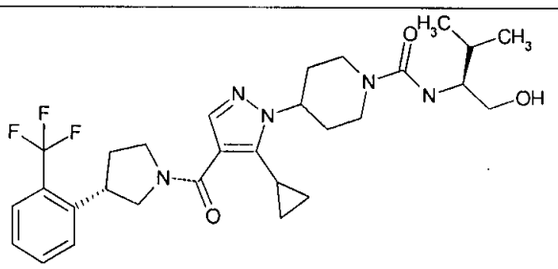
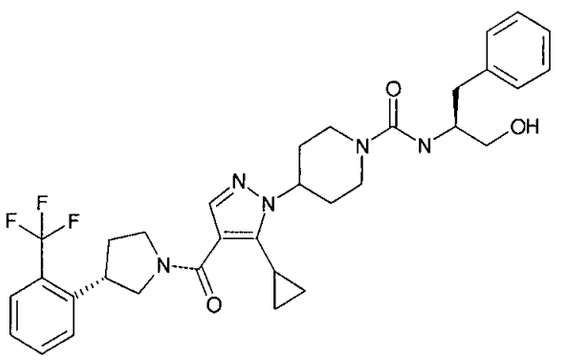
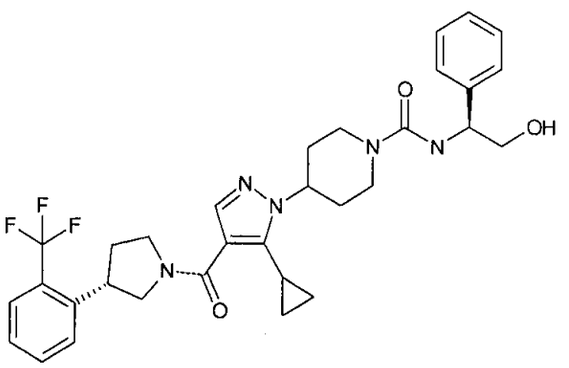
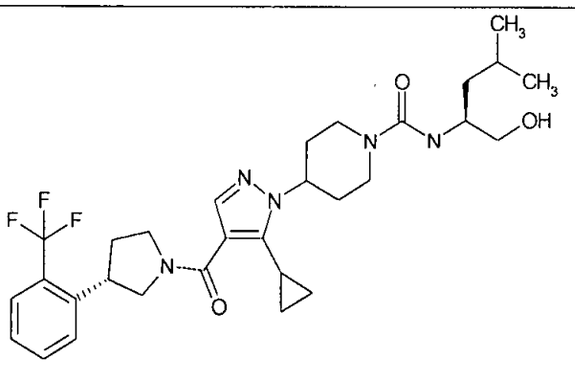
CUADRO 1-11

Ej. No.	Fórmula estructural	RMN
41		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.58-0.71 (2H; m); 0.92-1.03 (2H; m); 1.76-2.36 (8H; m); 2.70-2.80 (6H; brs); 2.81-3.03 (2H; m); 3.24-3.92 (13H; m); 4.52-4.71 (1H; m); 7.41-7.77 (5H; m); 10.76-10.91 (1H; brs)
42		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.58-0.74 (2H; m); 0.92-1.05 (2H; m); 1.60-2.00 (9H; m); 2.03-2.38 (2H; m); 2.65-3.93 (15H; m); 4.04-4.24 (2H; m); 4.51-4.73 (1H; m); 6.28-6.65 (1H; m); 7.41-7.81 (5H; m); 9.88 (1H; br s)
43		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.83 (2H; m); 1.02-1.15 (2H; m); 1.22-1.38 (2H; m); 1.70-2.26 (11H; m); 2.28-2.46 (1H; m); 2.67-2.79 (1H; m); 2.86-3.04 (2H; m); 3.10-3.24 (1H; m); 3.40-4.21 (9H; m); 4.32-4.45 (1H; m); 4.47-4.64 (2H; m); 7.32-7.72 (5H; m)
44		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.85 (2H; m); 1.02-1.18 (2H; m); 1.70-2.57 (11H; m); 2.91-3.08 (2H; m); 3.38-4.13 (11H; m); 4.74-4.66 (1H; m); 7.32-7.76 (5H; m)

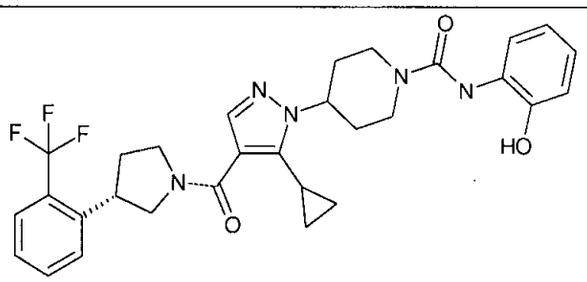
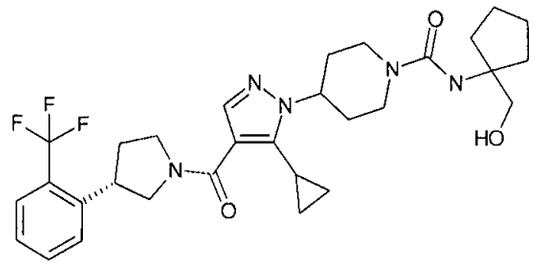
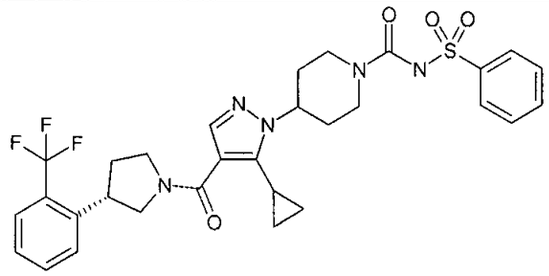
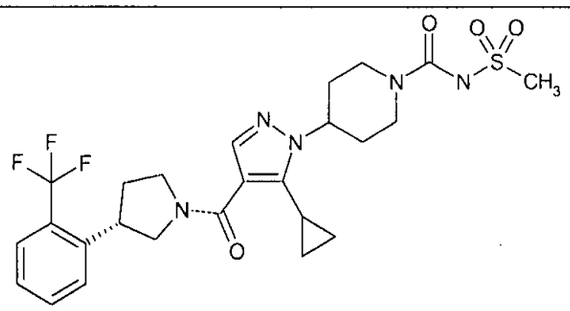
CUADRO 1-12

Ej. No.	Fórmula estructural	RMN
45		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.65-0.85 (2H; m); 0.96-1.17 (2H; m); 1.65-1.95 (3H; m); 1.96-2.22 (3H; m); 1.99 (3H; s); 2.25-2.48 (1H; m); 2.81-3.02 (2H; m); 3.38-3.5 (0.6H; m); 3.54-4.14 (8.4H; m); 4.19-4.37 (2H; m); 4.43-4.72 (2H; m); 6.24-6.40 (1H; m); 7.32-7.40 (1H; m); 7.41-7.61 (3H; m); 7.62-7.70 (1H; m)
46		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.88 (2H; m); 1.02-1.17 (2H; m); 1.71-1.87 (1H; m); 1.88-2.45 (6H; m); 2.48-2.60 (2H; m); 2.90-3.06 (2H; m); 3.43-4.11 (11H; m); 4.49-4.66 (1H; m); 7.33-7.72 (5H; m)
47		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.81 (2H; m); 1.01-1.12 (2H; m); 1.71-1.82 (1H; m); 1.83-1.96 (3H; m); 1.99-2.25 (3H; m); 2.26-2.43 (1H; m); 2.93-3.08 (2H; m); 3.41-4.00 (6H; m); 4.00-4.20 (2H; m); 4.49-4.64 (1H; m); 4.85-4.97 (1H; m); 7.30-7.70 (5H; m)
48		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.86 (2H; m); 1.01-1.17 (2H; m); 1.71-2.45 (7H; m); 2.86-3.06 (2H; m); 3.42-4.12 (11H; m); 4.49-4.67 (1H; m); 7.31-7.73 (5H; m)

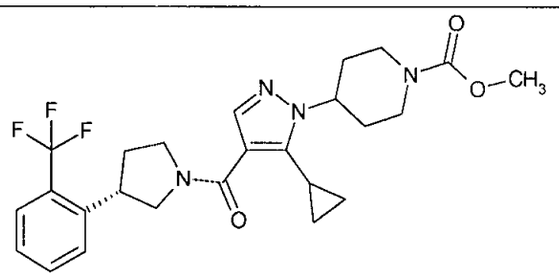
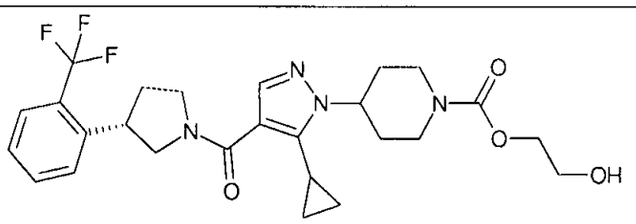
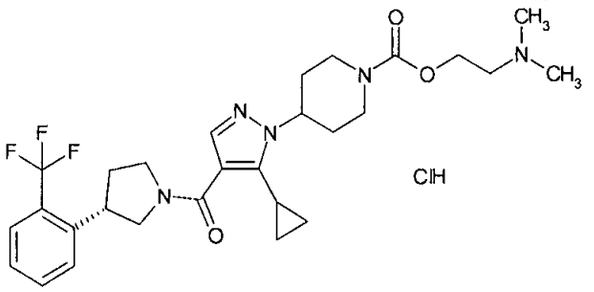
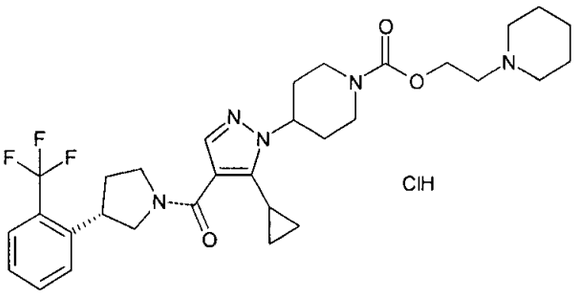
CUADRO 1-13

Ej. No.	Fórmula estructural	RMN
49		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.71-0.83 (2H;m); 0.92-1.02 (6H; m); 1.02-1.13 (2H; m); 1.22-1.33 (2H; m); 1.71-1.98 (4H;m); 1.99-2.45 (4H; m); 2.88-3.08 (2H; m); 3.14-3.28 (1H; brs); 3.38-4.24 (8H; m); 4.47-4.73 (2H; m); 7.32-7.72 (5H; m)
50		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.63-0.81 (2H; m); 0.96-1.13 (2H; m); 1.60-1.81 (3H; m); 1.90-2.21 (3H; m); 2.26-2.46 (1H; m); 2.72-2.98 (4H; m); 3.38-4.13 (9H; m); 4.37-4.59 (1H; m); 4.94-5.04 (1H; m); 7.16-7.73 (10H; m)
51		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.82 (2H; m); 1.00-1.12 (2H; m); 1.69-1.85 (3H; m); 1.96-2.22 (3H; m); 2.25-2.45 (1H; m); 2.84-3.01 (2H; m); 3.39-3.50 (2H; m); 3.54-4.27 (7H; m); 4.41-4.61 (1H; m); 4.93-5.04 (1H; m); 5.38-5.55 (1H; m); 7.23-7.73 (10H; m)
52		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.79 (2H; m); 0.89-0.99 (6H; m); 1.02-1.12 (2H; m); 1.31-1.43 (2H; m); 1.60-1.85 (4H; m); 2.00-2.20 (3H; m); 2.25-2.45 (1H; m); 2.81-3.00 (2H; m); 3.39-4.21 (10H; m); 4.42-4.60 (1H; m); 4.79-4.92 (1H; m); 7.30-7.73 (5H; m)

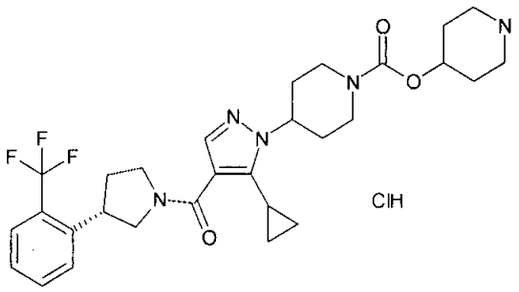
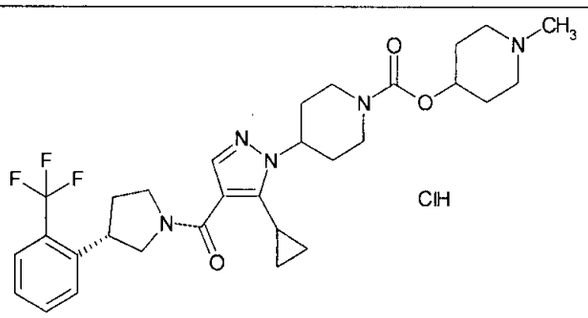
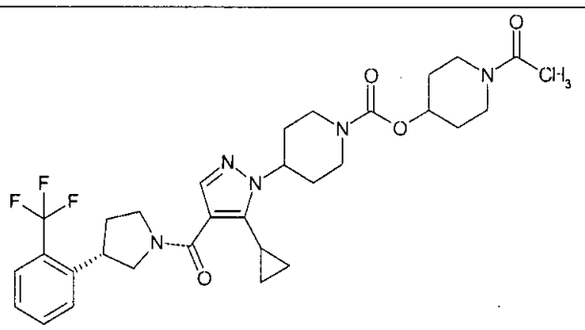
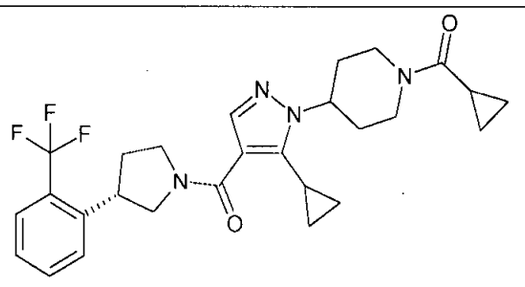
CUADRO 1-14

Ej. No.	Fórmula estructural	RMN
53		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.66-0.83 (2H; m); 1.00-1.14 (2H; m); 1.67-1.90 (3H; m); 1.98-2.27 (3H; m); 2.27-2.24 (1H; m); 2.98-3.14 (2H; m); 3.42-4.11 (5H; m); 4.22-4.40 (2H; m); 4.50-4.66 (1H; m); 6.78-6.88 (1H; m); 6.98-7.13 (3H; m); 7.14-7.21 (1H; m); 7.34-7.61 (4H; m); 7.64-7.73 (1H; m); 9.24-9.36 (1H; m)
54		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.67-0.85 (2H; m); 0.97-1.16 (2H; m); 1.51-2.46 (15H; m); 2.84-3.07 (2H; m); 3.42-4.19 (9H; m); 4.47-4.64 (1H; m); 4.65-4.75 (1H; m); 5.14-5.24 (1H; m); 7.31-7.73 (5H; m)
55		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.61-0.85 (2H; m); 0.95-1.18 (2H; m); 1.36-2.25 (7H; m); 2.25-2.44 (1H; m); 2.76-3.05 (2H; m); 3.38-3.47 (0.5H; m); 3.52-3.91 (3.5H; m); 3.95-4.31 (3H; m); 4.34-4.60 (1H; m); 7.29-7.73 (8H; m); 8.00-8.13 (2H; m)
56		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.63-0.83 (2H; m); 0.98-1.16 (2H; m); 1.65-1.91 (3H; m); 1.92-2.23 (3H; m); 2.24-2.50 (1H; m); 2.80-3.05 (2H; m); 3.16-3.34 (3H; m); 3.39-3.51 (0.6H; m); 3.52-4.13 (5.4H; m); 4.19-4.43 (2H; m); 4.44-4.64 (1H; m); 7.30-7.39 (1H; m); 7.41-7.60 (3H; m); 7.61-7.70 (1H; m)

CUADRO 1-15

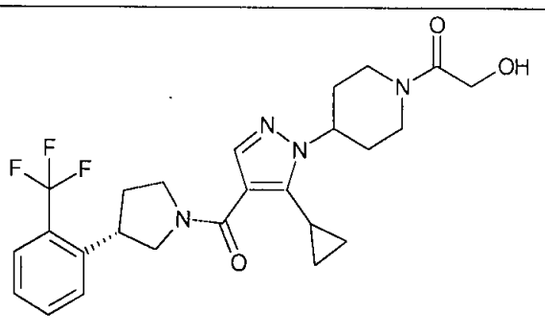
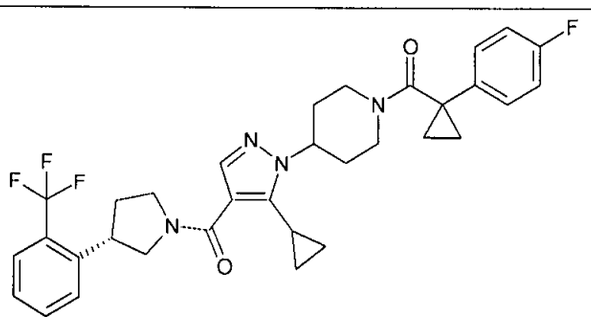
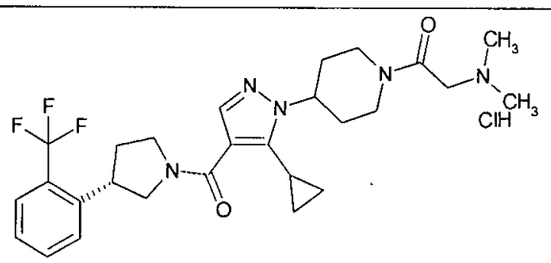
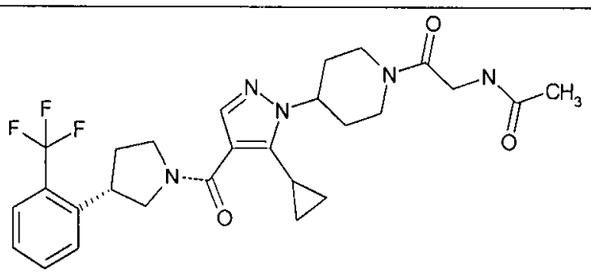
Ej. No.	Fórmula estructural	RMN
57		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.64-0.83 (2H; m); 0.98-1.15 (2H; m); 1.65-1.94 (3H; m); 1.94-2.25 (3H;m); 2.25-2.45 (1H; m); 2.77-3.05 (2H; m); 3.43-4.07 (8H; m); 4.11-4.45 (2H; m); 4.45-4.65 (1H; m); 7.30-7.72 (5H; m)
58		^{1}H-RMN (400MHz; DMSO-D6) δ: 0.67-0.84 (2H; m); 1.03-1.15 (2H; m); 1.69-2.59 (8H; m); 2.86-3.11 (2H; m); 3.38-4.13 (7H; m); 4.19-4.44 (4H; m); 4.48-4.66 (1H; m); 7.30-7.74 (5H; m)
59		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.64-0.87 (2H; m); 0.99-1.18 (2H; m); 1.72-1.86 (1H; m); 1.87-1.99 (2H; m); 2.06-2.47 (4H; m); 2.63-3.23 (10H; m); 3.26-3.42 (2H; m); 3.43-4.13 (3H; m); 4.20-4.75 (5H; m); 7.33-7.39 (1H; m); 7.40-7.63 (3H; m); 7.64-7.69 (1H; m); 12.69 (1H; brs)
60		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.72-0.83 (2H; m); 1.07-1.23 (2H; m); 1.35-1.56 (1H; m); 1.79-2.00 (4H; m); 2.06-2.45 (6H; m); 2.68-3.20 (4H; m); 3.27-3.41 (2H; m); 3.43-4.08 (9H; m); 4.22-4.48 (2H; m); 4.58-4.82 (3H; m); 7.34-7.40 (1H; m); 7.44-7.50 (1H; m); 7.53-7.60 (1H; m); 7.65-7.72 (2H; m); 12.22 (1H; brs)

CUADRO 1-16

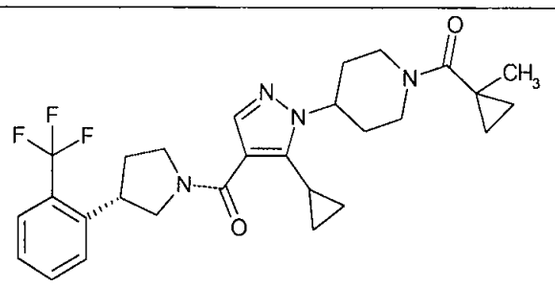
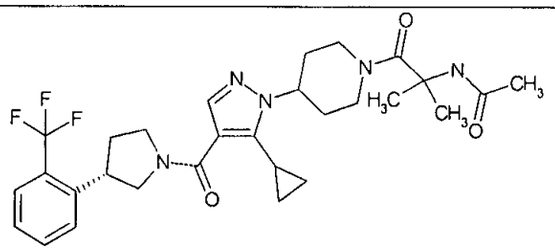
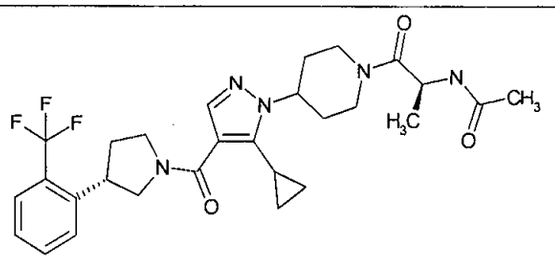
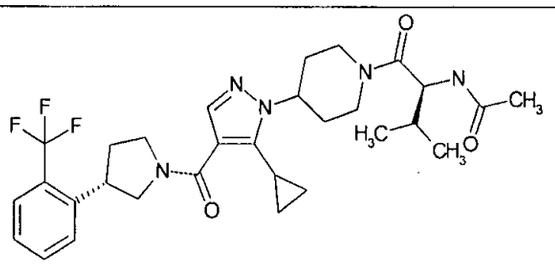
Ej. No.	Fórmula estructural	RMN
61		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.88 (2H; m); 1.03-1.21 (2H; m); 1.79-2.01 (3H; m); 2.01-2.32 (7H; m); 2.33-2.45 (1H; m); 2.81-3.12 (2H; m); 3.11-4.14 (9H; m); 4.15-4.49 (2H; m); 4.54-4.75 (1H; m); 4.92-5.09 (1H; m); 7.33-7.41 (1H; m); 7.44-7.61 (2H; m); 7.63-7.75 (2H; m); 9.45-9.81 (2H; m)
62		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.87 (2H; m); 1.04-1.21 (2H; m); 1.78-2.01 (3H; m); 2.03-2.49 (7H; m); 2.50-2.68 (1H; m); 2.72-3.14 (7H; m); 3.23-4.07 (7H; m); 4.17-4.44 (2H; m); 4.57-4.75 (1H; m); 4.76-4.89 (0.5H; m); 5.01-5.09 (0.5H; m); 7.33-7.41 (1H; m); 7.43-7.52 (1H; m); 7.52-7.61 (1H; m); 7.62-7.73 (2H; m); 12.38-12.70 (1H; m)
63		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.66-0.85 (2H; m); 0.99-1.16 (2H; m); 1.57-2.25 (13H; m); 2.26-2.46 (1H; m); 2.79-3.11 (2H; m); 3.27-3.54 (2.6H; m); 3.55-4.12 (6.4H; m); 4.14-4.66 (3H; m); 4.85-5.00 (1H; m); 7.31-7.40 (1H; m); 7.41-7.61 (3H; m); 7.62-7.71 (1H; m)
64		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.64-0.87 (4H; m); 0.91-1.18 (4H; m); 1.70-1.86 (2H; m); 1.88-2.48 (6H; m); 2.65-2.89 (1H; m); 3.13-3.39 (1H; m); 3.41-4.13 (5H; m); 4.27-4.89 (3H; m); 7.31-7.76 (5H; m)

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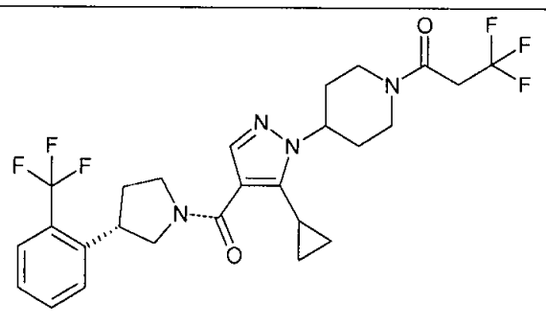
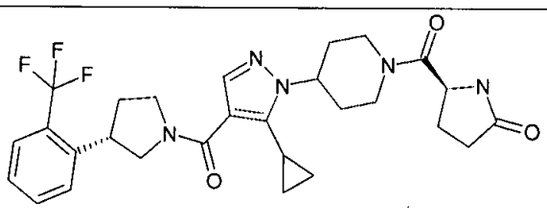
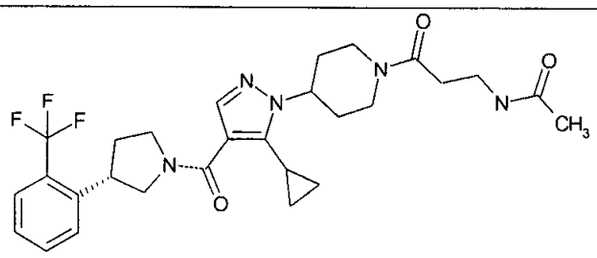
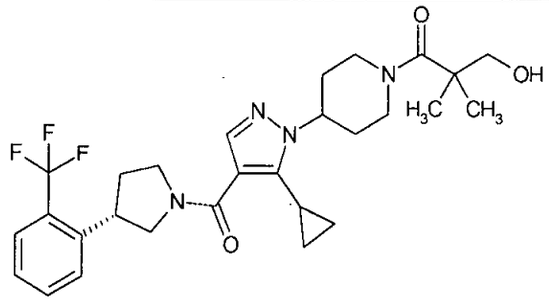
CUADRO 1-17

Ej. No.	Fórmula estructural	RMN
65		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.87 (2H; m); 1.01-1.16 (2H; m); 1.69-1.86 (1H; m); 1.90-2.49 (6H; m); 2.85-3.02 (1H; m); 3.07-3.26 (1H; m); 3.40-4.12 (7H; m); 4.16-4.29 (2H; m); 4.54-4.82 (2H; m); 7.31-7.77 (5H; m)
66		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.63-0.83 (2H; m); 0.98-1.10 (2H; m); 1.12-1.23 (2H; m); 1.38-1.51 (2H; m); 1.66-2.22 (6H; m); 2.27-2.45 (1H; m); 2.73-3.03 (2H; m); 3.37-4.11 (5H; m); 4.15-4.95 (3H; m); 6.94-7.73 (9H; m)
67		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.60-0.74 (2H; m); 0.92-1.06 (2H; m); 1.15-1.20 (1H; m); 1.75-2.36 (4H; m); 2.78-2.87 (6H; brs); 3.14-3.36 (1H; m); 3.40-3.92 (9H; m); 4.22-4.56 (3H; m); 4.64-4.86 (1H; m); 7.40-7.62 (2H; m); 7.64-7.77 (3H; m); 9.61-9.74 (1H; brs)
68		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.72-0.84 (2H; m); 1.04-1.16 (2H; m); 1.72-1.86 (1H; m); 1.90-2.28 (8H; m); 2.28-2.45 (1H; m); 2.81-2.96 (1H; m); 3.15-3.29 (1H; m); 3.42-3.51 (0.5H; m); 3.58-4.21 (7.5H; m); 4.58-4.79 (2H; m); 6.58-6.67 (1H; br s); 7.33-7.42 (1H; m); 7.42-

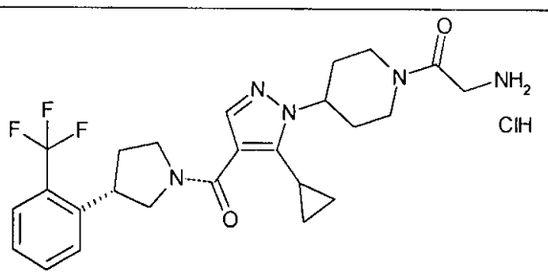
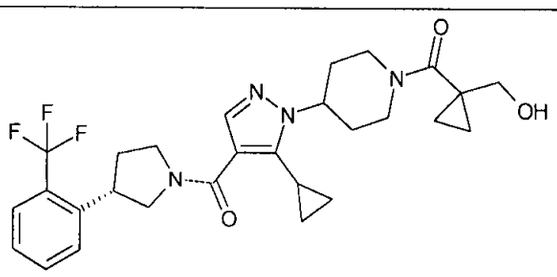
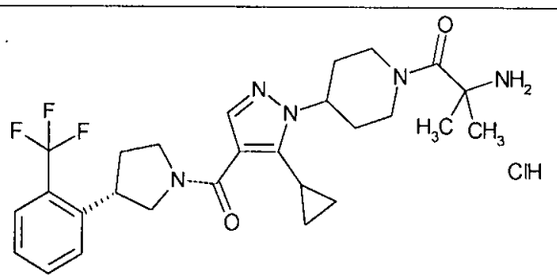
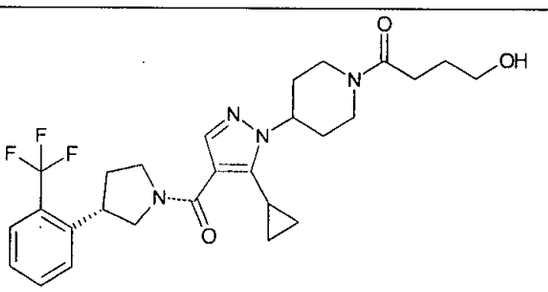
CUADRO 1-18

Ej. No.	Fórmula estructural	RMN
69		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.54-0.67 (2H; m); 0.71-0.86 (2H; m); 0.92-1.02 (2H; m); 1.04-1.14 (2H; m); 1.28-1.40 (3H; m); 1.72-1.86 (1H; m); 1.89-2.24 (5H; m); 2.27-2.46 (1H; m); 2.86-3.13 (2H; m); 3.41-4.12 (5H; m); 4.51-4.71 (3H; m); 7.32-7.75 (5H; m)
70		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.82 (2H; m); 1.01-1.12 (2H; m); 1.60-1.71 (7H; m); 1.71-2.45 (10H; m); 2.93-3.12 (1H; m); 3.37-4.10 (6H; m); 4.47-4.70 (2H; m); 6.70-6.79 (1H; brs); 7.28-7.71 (5H; m)
71		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.84 (2H; m); 1.02-1.13 (2H; m); 1.29-1.41 (4H; m); 1.71-1.84 (1H; m); 1.89-2.45 (7H; m); 2.76-2.96 (2H; m); 3.16-3.34 (2H; m); 3.39-4.15 (5H; m); 4.56-4.79 (2H; m); 4.85-4.99 (1H; m); 6.55-6.67 (1H; m); 7.31-7.70 (5H; m)
72		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.83 (2H; m); 0.84-1.03 (6H; m); 1.03-1.14 (2H; m); 1.22-1.34 (2H; m); 1.71-2.44 (9H; m); 2.76-2.92 (1H; m); 3.17-4.79 (9H; m); 4.84-4.95 (1H; m); 6.19-6.30 (1H; m); 7.31-7.71 (5H; m)

CUADRO 1-19

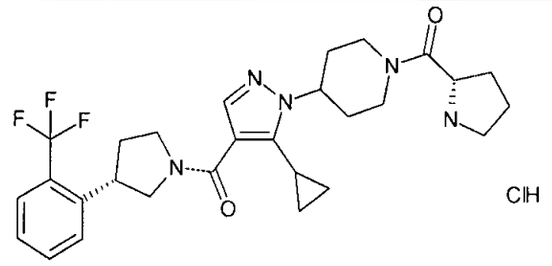
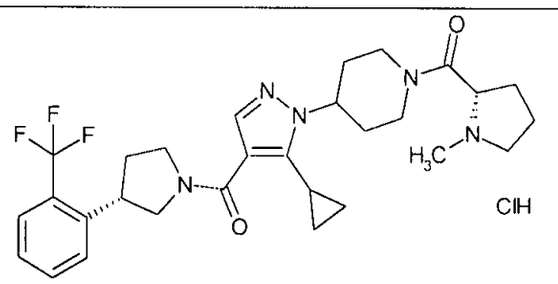
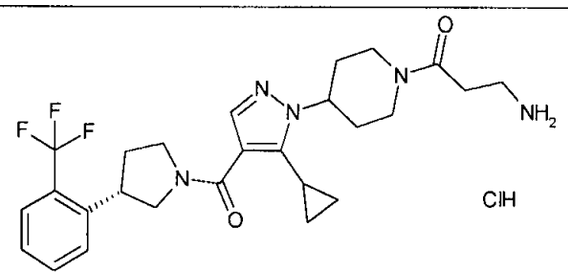
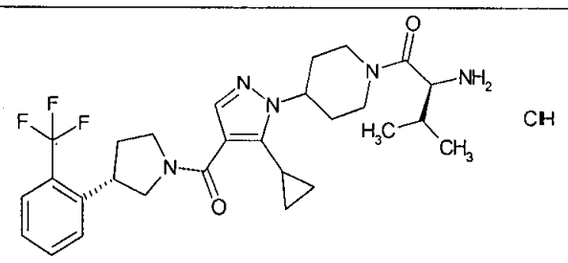
Ej. No.	Fórmula estructural	RMN
73		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.66-0.86 (2H; m); 0.99-1.18 (2H; m); 1.69-1.85 (1H; m); 1.89-2.45 (6H; m); 2.78-2.94 (1H; m); 3.19-3.39 (3H; m); 3.41-3.50 (0.6H; m); 3.56-4.10 (5.4H; m); 4.56-4.83 (2H; m); 7.32-7.40 (1H; m); 7.41-7.61 (3H; m); 7.62-7.71 (1H; m)
74		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.67-0.85 (2H; m); 1.03-1.15 (2H; m); 1.69-1.86 (1H; m); 1.91-2.61 (9H; m); 2.76-2.95 (1H; m); 3.18-4.11 (8H; m); 4.44-4.83 (3H; m); 5.76-5.93 (1H; m); 7.32-7.75 (5H; m)
75		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.82 (2H; m); 1.02-1.13 (2H; m); 1.69-1.84 (1H; m); 1.85-2.01 (6H; m); 2.02-2.23 (2H; m); 2.26-2.46 (1H; m); 2.47-2.60 (2H; m); 2.71-2.84 (1H; m); 3.11-3.26 (1H; m); 3.41-4.10 (8H; m); 4.54-4.68 (1H; m); 4.69-4.82 (1H; m); 6.32-6.40 (1H; brs); 7.31-7.70 (5H; m)
76		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.87 (2H; m); 1.02-1.18 (2H; m); 1.31 (3H; s); 1.33 (3H; s); 1.72-1.88 (1H; m); 1.90-2.48 (6H; m); 2.88-3.10 (2H; m); 3.42-4.15 (8H; m); 4.47-4.75 (3H; m); 7.32-7.74 (5H; m)

CUADRO 1-20

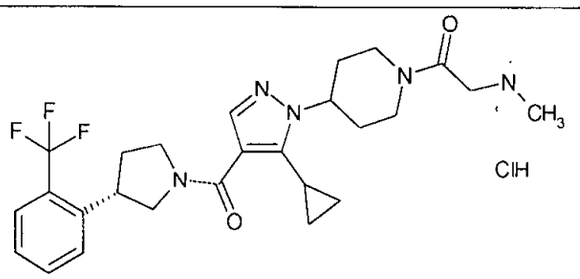
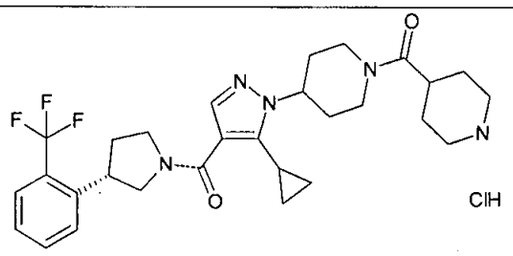
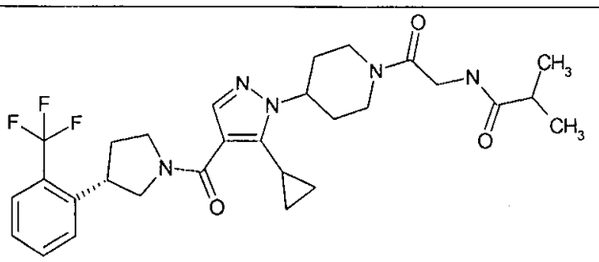
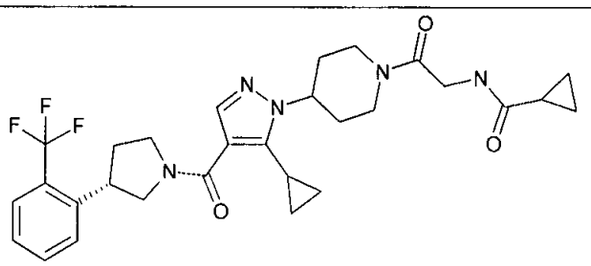
Ej. No.	Fórmula estructural	RMN
77		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.59-0.74 (2H; m); 0.93-1.05 (2H; m); 1.21-1.32 (1H; m); 1.72-2.34 (5H; m); 2.79-2.98 (1H;m); 3.13-3.34 (1H; m); 3.39-4.36 (9H; m); 4.38-4.55 (1H; m); 4.63-4.84 (1H; m); 7.40-7.60 (2H; m); 7.63-7.74 (3H; m); 8.80-8.18 (3H; brs)
78		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.89 (4H; m); 0.97-1.16 (4H; m); 1.71-1.86 (1H; m); 1.88-2.24 (6H; m); 2.27-2.46 (1H; m); 2.90-3.11 (2H; m); 3.41-4.11 (7H; m); 4.54-4.74 (3H; m); 7.33-7.74 (5H; m)
79		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.60-0.74 (2H; m); 0.94-1.03 (2H; m); 1.50-1.65 (7H; m); 1.74-2.38 (5H; m); 2.99-3.28 (2H;m); 3.37-3.90 (5H; m); 3.94-4.65 (3H; m); 4.67-4.89 (1H; m); 7.40-7.78 (5H; m); 8.12-8.32 (3H; brs)
80		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.83 (2H; m); 1.02-1.14 (2H; m); 1.70-1.85 (1H; m); 1.85-2.46 (8H; m); 2.49-2.60 (2H; m); 2.69-2.85 (2H; m); 3.13-3.29 (1H; m); 3.41-3.50 (0.5H; m); 3.55-4.14 (7.5H; m); 4.53-4.70 (1H; m); 4.71-4.85 (1H; m); 7.31-7.40 (1H; m); 7.40-7.61 (3H; m); 7.62-7.73

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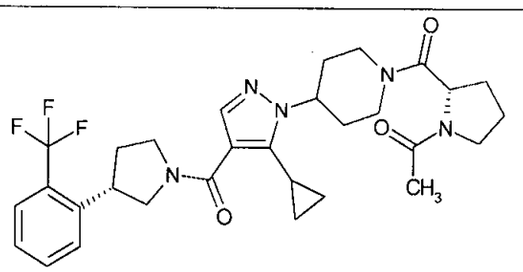
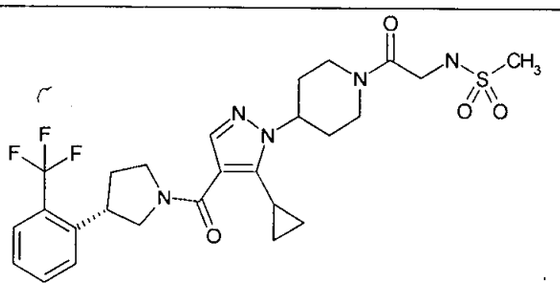
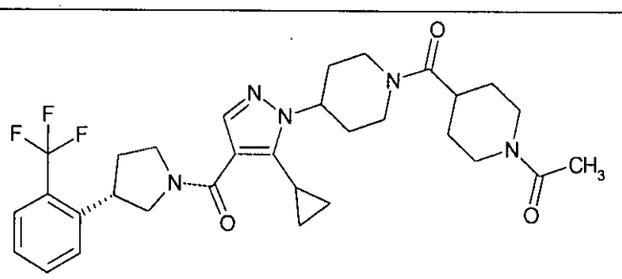
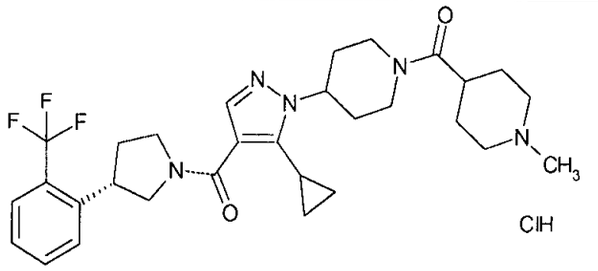
CUADRO 1-21

Ej. No.	Fórmula estructural	RMN
81		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.58-0.74 (2H; m); 0.93-1.10 (2H; m); 1.70-2.48 (12H; m); 2.83-3.03 (1H; m); 3.11-4.08 (9H; m); 4.41-4.85 (2H; m); 7.42-7.53 (2H; m); 7.65-7.78 (3H; m); 9.91-10.05 (1H; brs); 10.12-10.24 (1H; brs)
82		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.60-0.75 (2H; m); 0.92-1.03 (2H; m); 1.74-2.17 (11H; m); 2.18-2.35 (1H; m); 2.73-2.87 (3H; m); 2.88-3.90 (10H; m); 4.43-4.56 (1H; m); 4.60-4.85 (1H; m); 7.41-7.76 (5H; m); 9.53-9.70 (1H; brs)
83		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.58-0.72 (2H; m); 0.93-1.04 (2H; m); 1.69-2.02 (5H; m); 2.03-2.16 (1H; m); 2.17-2.34 (1H; m); 2.64-2.87 (3H; m); 2.91-3.07 (2H; m); 3.16-3.32 (1H; m); 3.42-3.78 (6H; m); 3.80-3.99 (1H; m); 4.44-4.58 (1H; m); 7.42-7.94 (8H; m)
84		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.60-0.73 (2H; m); 0.87-1.10 (8H; m); 1.73-2.17 (8H; m); 2.18-2.34 (1H; m); 2.81-2.98 (1H; m); 3.21-3.37 (1H; m); 3.40-3.92 (4H; m); 4.04-4.19 (1H; m); 4.23-4.41 (1H; m); 4.46-4.61 (1H; m); 4.66-4.85 (1H; m); 7.43-7.61 (2H; m); 7.64-7.77 (3H; m); 8.07-8.24 (3H; m)

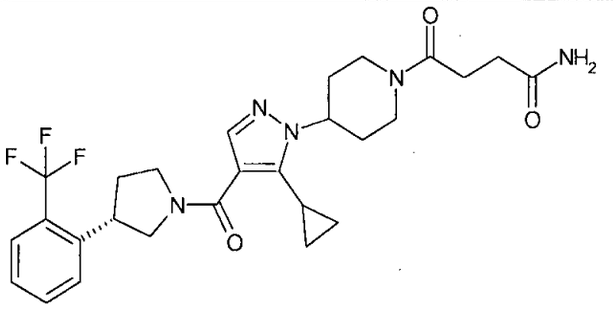
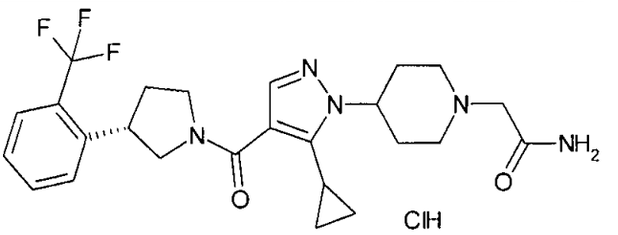
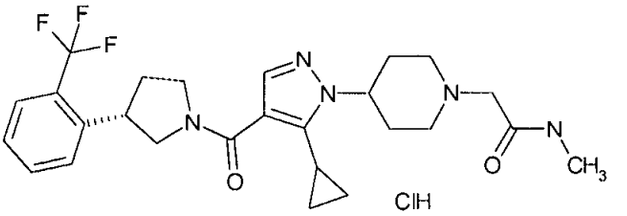
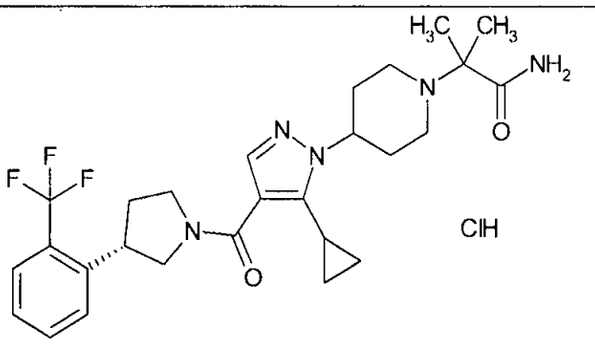
CUADRO 1-22

Ej. No.	Fórmula estructural	RMN
85		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.60-0.74 (2H; m); 0.92-1.06 (2H; m); 1.72-2.35 (8H; m); 2.53-2.62 (3H; m); 2.80-2.98 (1H; m); 3.18-3.34 (1H; m); 3.42-3.90 (5H; m); 3.98-4.23 (2H; m); 4.40-4.54 (1H; m); 4.66-4.82 (1H; m); 7.42-7.78 (5H; m); 8.77-9.02 (2H; m)
86		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.59-0.72 (2H; m); 0.93-1.02 (2H; m); 1.67-1.84 (6H; m); 1.85-2.00 (4H; m); 2.03-2.17 (1H; m); 2.18-2.33 (1H; m); 2.65-2.81 (1H; m); 2.84-3.08 (3H; m); 3.16-3.32 (4H; m); 3.52-3.90 (3H; m); 4.05-4.19 (1H; m); 4.44-4.57 (1H; m); 4.63-4.79 (1H; m); 7.40-7.75 (5H; m); 8.62-8.78 (1H; m); 9.04-9.16 (1H; m)
87		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.84 (2H; m); 1.03-1.12 (2H; m); 1.14-1.22 (7H; m); 1.66-2.24 (6H; m); 2.27-2.54 (2H; m); 2.79-2.96 (1H; m); 3.13-3.27 (1H; m); 3.39-3.50 (1H; m); 3.55-4.18 (6H; m); 4.53-4.79 (2H; m); 6.58-6.61 (1H; m); 7.31-7.71 (5H; m)
88		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.83 (4H; m); 0.92-1.01 (2H; m); 1.01-1.13 (2H; m); 1.45-1.54 (1H; m); 1.68-2.44 (8H; m); 2.80-2.95 (1H; m); 3.12-3.29 (1H; m); 3.41-3.50 (1H; m); 3.57-4.22 (6H; m); 4.56-4.79 (2H; m);

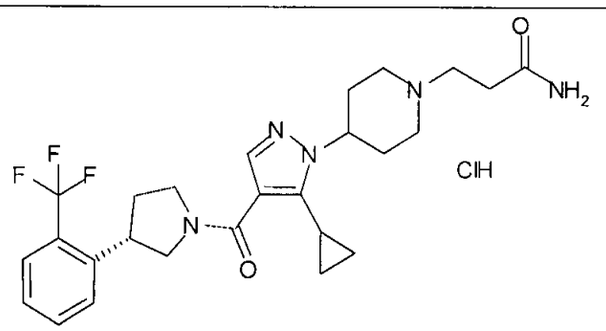
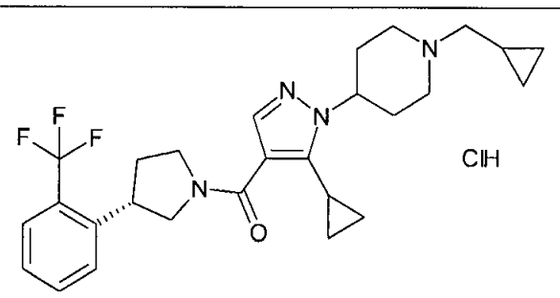
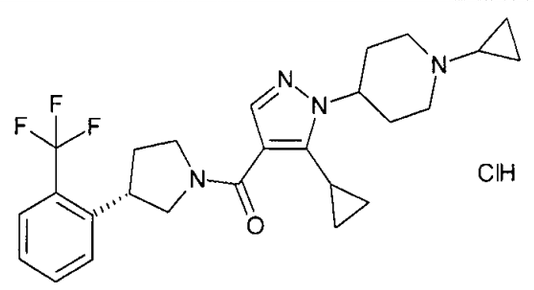
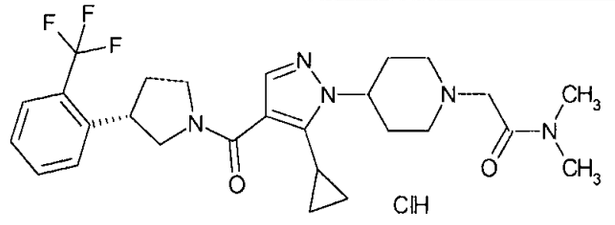
CUADRO 1-23

Ej. No.	Fórmula estructural	RMN
89		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.71-0.82 (2H; m); 1.03-1.14 (2H; m); 1.70-1.84 (1H; m); 1.85-2.25 (12H; m); 2.25-2.42 (1H; m); 2.75-2.95 (1H; m); 3.18-4.21 (9H; m); 4.54-4.78 (2H; m); 4.87-4.97 (1H; m); 7.32-7.71 (5H; m)
90		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.85 (2H; m); 1.02-1.16 (2H; m); 1.70-1.86 (1H; m); 1.89-2.45 (6H; m); 2.83-2.96 (1H; m); 2.96-3.03 (3H; m); 3.16-3.31 (1H; m); 3.41-3.50 (0.6H; m); 3.56-4.12 (7.4H; m); 4.57-4.77 (2H; m); 5.35-5.44 (1H; m); 7.32-7.40 (1H; m); 7.41-7.61 (3H; m); 7.62-7.71 (1H; m)
91		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.71-0.81 (2H; m); 1.04-1.12 (2H; m); 1.62-2.44 (11H; m); 2.09 (3H; brs); 2.66-2.82 (3H; m); 3.05-3.17 (1H; m); 3.18-3.31 (1H; m); 3.39-3.50 (1H; m); 3.55-3.99 (5H; m); 4.00-4.15 (1H; m); 4.51-4.70 (2H; m); 4.71-4.84 (1H; m); 7.31-7.70 (5H; m)
92		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.59-0.72 (2H; m); 0.93-1.05 (2H; m); 1.67-2.02 (11H; m); 2.04-2.16 (1H; m); 2.18-2.34 (1H; m); 2.66-2.75 (3H; brs); 2.86-3.01 (2H; m); 3.09-3.32 (1H; m); 3.36-3.91 (6H; m); 3.99-4.16 (1H; m); 4.44-4.58 (2H; m); 4.63-4.80 (1H;

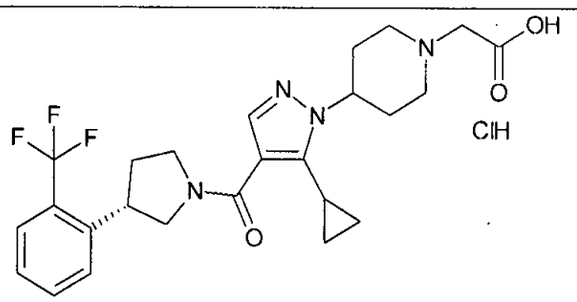
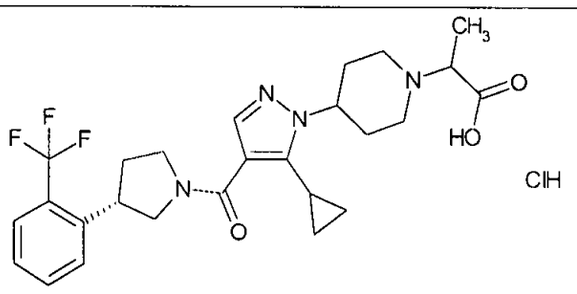
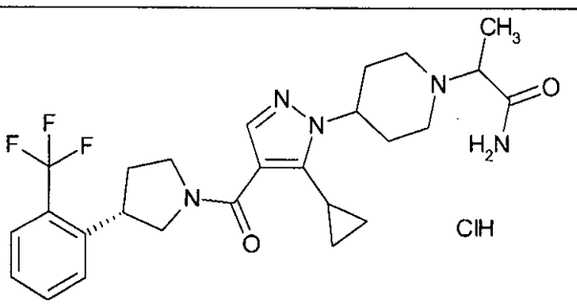
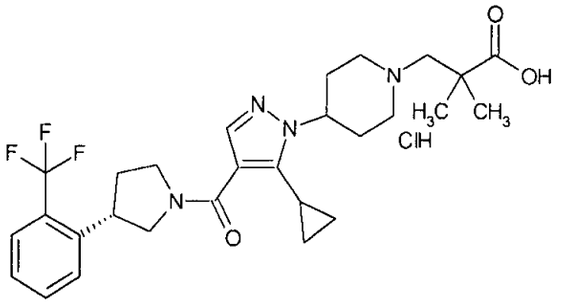
CUADRO 1-24

Ej. No.	Fórmula estructural	RMN
93		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.84 (2H; m); 1.03-1.12 (2H; m); 1.14-1.22 (7H; m); 1.66-2.24 (6H; m); 2.27-2.54 (2H; m); 2.79-2.96 (1H; m); 3.13-3.27 (1H; m); 3.39-3.50 (1H; m); 3.55-4.18 (6H; m); 4.53-4.79 (2H; m); 6.58-6.61 (1H; m); 7.31-7.71 (5H; m)
94		^{1}H-RMN (400MHz; DMSO-d_6) δ: 0.57-0.73 (2H; m); 0.90-1.05 (2H; m); 1.82-2.53 (8H; m); 3.23-3.79 (6H; m); 3.81-4.24 (4H; m); 4.63-4.97 (1H; m); 7.39-7.77 (6H; m); 7.98-8.17 (1H; m); 9.99-10.27 (1H; m)
95		^{1}H-RMN (400MHz; DMSO-d_6) δ: 0.59-0.75 (2H; m); 0.91-1.07 (2H; m); 1.82-2.46 (8H; m); 2.64-2.76 (3H; m); 3.21-3.99 (10H; m); 4.61-4.82 (1H; m); 7.41-7.79 (5H; m); 8.48-8.69 (1H; m); 9.99-10.24 (1H; m)
96		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.61-0.82 (2H; m); 1.02-1.18 (2H; m); 1.69 (6H; s); 1.70-1.84 (1H; m); 2.05-2.23 (3H; m); 2.29-2.46 (1H; m); 3.03-4.07 (11H; m); 5.02 (1H; brs); 5.74 (1H; brs); 7.34-7.41 (1H; m); 7.44-7.50 (1H; m); 7.51-7.60 (2H; m); 7.65-7.70 (1H; m); 9.13 (1H; brs); 11.80 (1H; brs)

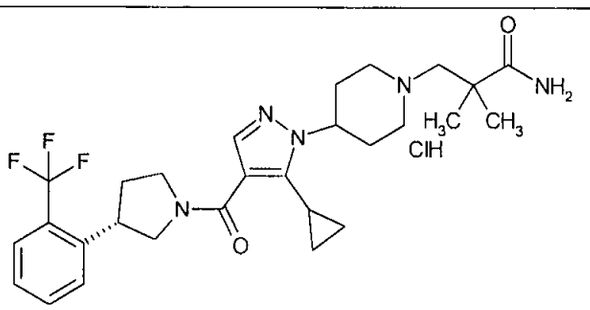
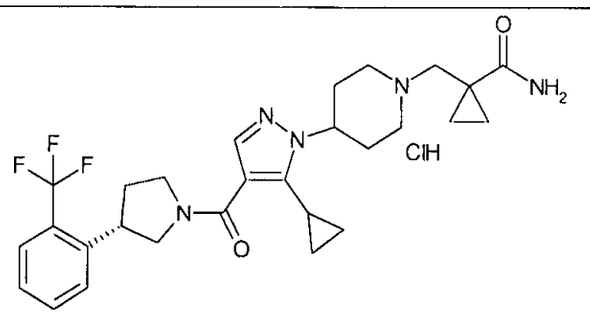
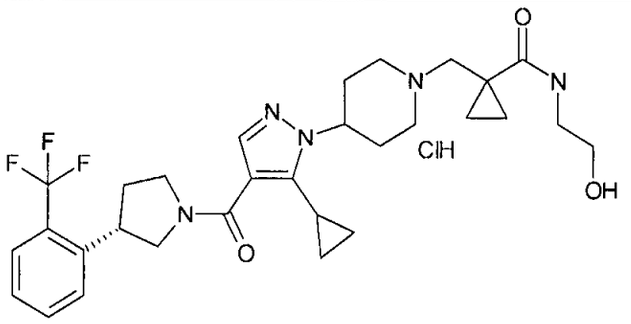
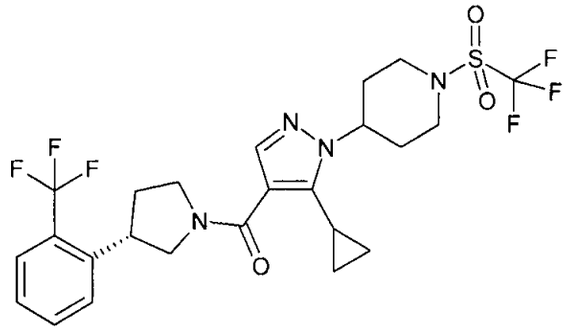
CUADRO 1-25

Ej. No.	Fórmula estructural	RMN
97		^{1}H-RMN (400MHz; DMSO-d_6) δ: 0.58-0.77 (2H; m); 0.90-1.06 (2H; m); 1.83-1.98 (1H; m); 2.04-2.74 (6H; m); 3.07-3.96 (13H; m); 4.64-4.97 (1H; m); 7.20-7.85 (7H; m); 10.09-10.49 (1H; m)
98		^{1}H-RMN (400MHz; DMSO-d_6) δ: 0.30-0.49 (2H; m); 0.56-0.76 (4H; m); 0.88-1.05 (2H; m); 1.07-1.22 (1H; m); 1.81-1.98 (1H; m); 1.99-2.38 (6H; m); 2.88-3.04 (2H; m); 3.09-3.26 (2H; m); 3.41-3.95 (7H; m); 4.58-4.86 (1H; m); 7.34-7.85 (5H; m); 10.17-10.53 (1H; m)
99		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.60-0.74 (2H; m); 0.75-0.85 (2H; m); 0.93-1.04 (2H; m); 1.12-1.23 (2H; m); 1.86-2.54 (7H; m); 2.71-2.82 (1H; m); 3.28-3.92 (9H; m); 4.66-4.83 (1H; m); 7.42-7.77 (5H; m); 10.60-10.79 (1H; m)
100		^{1}H-RMN (400MHz; DMSO-d_6) δ: 0.57-0.75 (2H; m); 0.91-1.05 (2H; m); 1.82-2.53 (7H; m); 2.85-3.01 (6H; m); 3.18-4.44 (11H; m); 4.62-4.83 (1H; m); 7.41-7.78 (5H; m); 9.66-9.97 (1H; br)

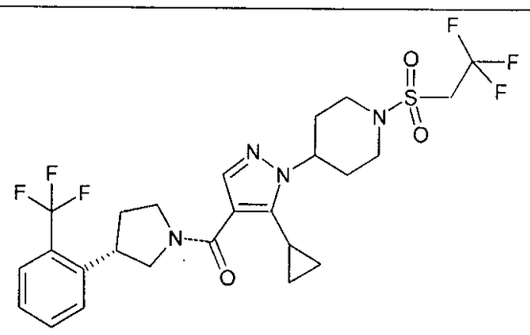
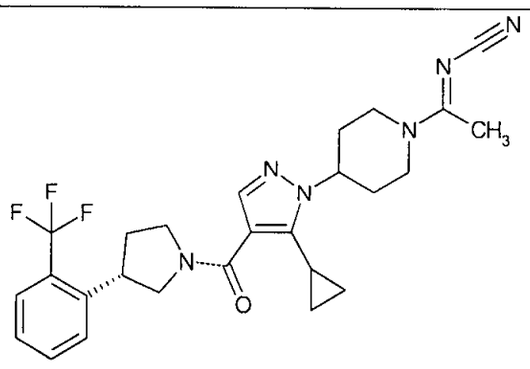
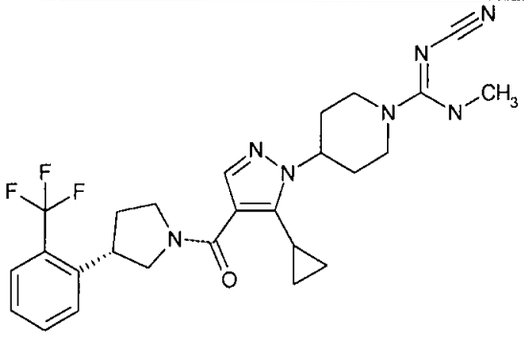
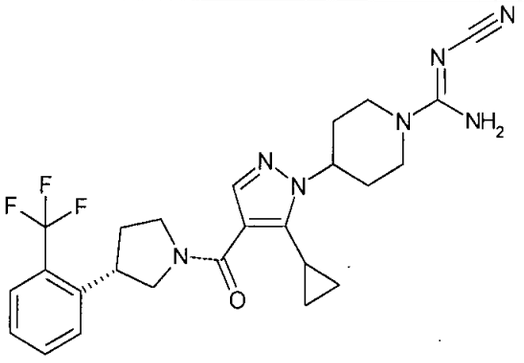
CUADRO 1-26

Ej. No.	Fórmula estructural	RMN
101		^{1}H-RMN (400MHz; DMSO-d_6) δ: 0.59-0.75 (2H; m); 0.91-1.06 (2H; m); 1.84-2.00 (1H; m); 2.03-2.45 (6H; m); 3.15-3.95 (9H; m); 4.06-4.23 (2H; m); 4.63-4.83 (1H; m); 7.41-7.80 (5H; m)
102		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.59-0.75 (2H; m); 0.91-1.06 (2H; m); 1.46-1.62 (4H; m); 1.84-2.60 (7H; m); 3.23-3.94 (7H;m); 4.16-4.32 (1H; m); 4.51-5.06 (2H; m); 7.40-7.79 (6H; m); 10.11-10.42 (1H; brs)
103		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.60-0.73 (2H; m); 0.92-1.04 (2H; m); 1.43-1.54 (3H; m); 2.00-2.58 (8H; m); 3.14-4.17 (9H; m); 4.68-4.85 (1H; m); 7.42-7.79 (6H; m); 8.08-8.20 (1H; m); 10.09 (1H; brs)
104		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.61-0.75 (2H; m); 0.94-1.06 (2H; m); 1.22-1.38 (6H; m); 1.82-2.62 (7H; m); 3.13-3.96 (11H; m); 4.69-4.95 (1H; m); 7.38-7.82 (6H; m); 9.23-9.88 (1H; m)

CUADRO 1-27

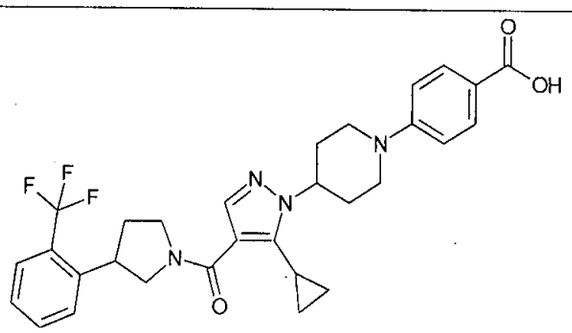
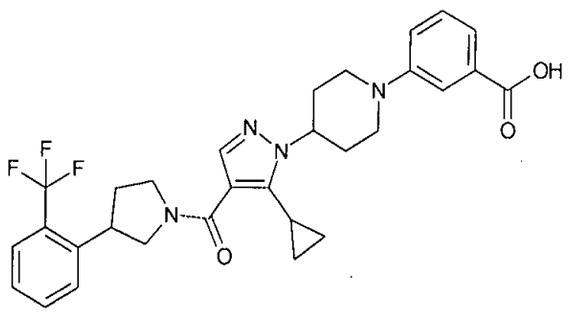
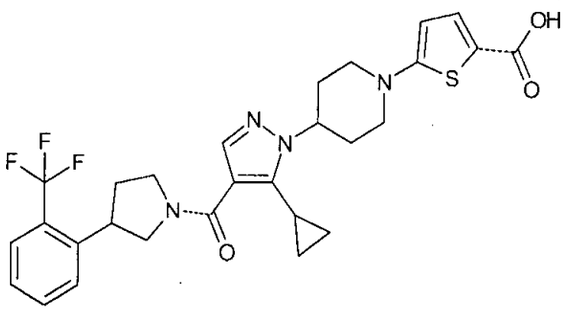
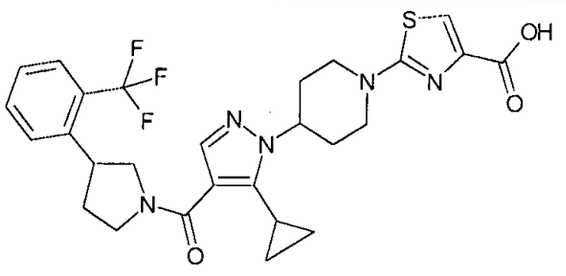
Ej. No.	Fórmula estructural	RMN
105		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.59-0.75 (2H; m); 0.93-1.06 (2H; m); 1.22-1.38 (6H; m); 1.83-1.98 (1H; m); 1.99-2.62 (6H; m); 3.14-3.94 (11H; m); 4.69-4.93 (1H; m); 7.27-7.80 (7H; m); 9.05-9.52 (1H; m)
106		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.56-0.77 (2H; m); 0.91-1.07 (2H; m); 1.15-1.39 (4H; m); 1.82-2.62 (7H; m); 3.13-4.03 (11H; m); 4.63-4.97 (1H; m); 7.06-7.32 (2H; m); 7.40-7.81 (5H; m); 9.76-10.08 (1H; m)
107		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.61-0.74 (2H; m); 0.93-1.04 (2H; m); 1.13-1.21 (2H; m); 1.25-1.34 (2H; m); 1.85-1.98 (1H; m); 2.01-2.54 (6H; m); 3.08-3.92 (16H; m); 4.64-4.84 (1H; m); 7.43-7.78 (6H; m); 9.57-9.92 (1H; m)
108		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.67-0.82 (2H; m); 1.01-1.14 (2H; m); 1.66-1.83 (1H; m); 1.94-2.44 (6H; m); 3.18-3.49 (2H; m); 3.54-4.20 (7H; m); 4.53-4.70 (1H; m); 7.28-7.72 (5H; m)

CUADRO 1-28

Ej. No.	Fórmula estructural	RMN
109		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.65-0.83 (2H; m); 0.99-1.11 (2H; m); 1.68-1.83 (1H; m); 1.91-2.45 (6H; m); 3.04-3.20 (2H; m); 3.38-4.11 (9H; m); 4.47-4.66 (1H; m); 7.72-8.35 (5H; m)
110		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.64-0.88 (2H; m); 0.98-1.21 (2H; m); 1.66-1.88 (1H; m); 1.89-2.54 (9H; m); 2.94-3.17 (1H; m); 3.26-3.53 (1.5H; m); 3.54-4.21 (5.5H; m); 4.58-4.93 (2H; m); 7.29-7.75 (5H; m)
111		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.62-0.83 (2H; m); 0.97-1.17 (2H; m); 1.63-1.95 (3H; m); 1.96-2.24 (3H; m); 2.25-2.47 (1H; m); 2.97-3.19 (5H; m); 3.40-3.49 (0.5H; m); 3.55-4.26 (6.5H; m); 4.46-4.69 (1H; m); 5.54-5.76 (1H; m); 7.30-7.60 (4H; m); 7.61-7.73 (1H; m)
112		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.60-0.81 (2H; m); 0.98-1.16 (2H; m); 1.62-1.82 (3H; m); 1.93-2.25 (3H; m); 2.26-2.47 (1H; m); 2.90-3.08 (2H; m); 3.35-3.50 (0.5H; m); 3.53-4.09 (4.5H; m); 4.17-4.34 (2H; m); 4.45-4.65 (1H; m); 5.94-6.14 (2H; m); 7.29-7.61 (4H; m); 7.62-7.74 (1H; m)

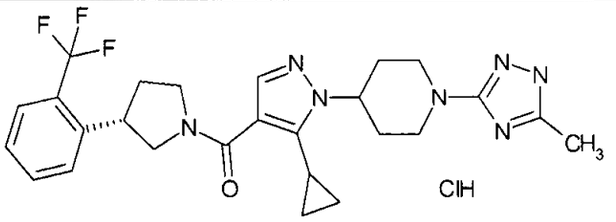
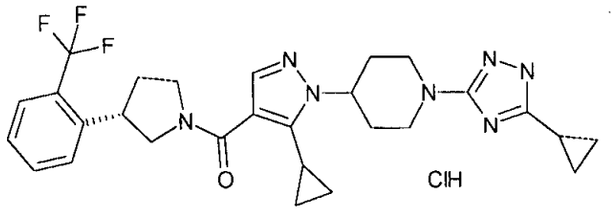
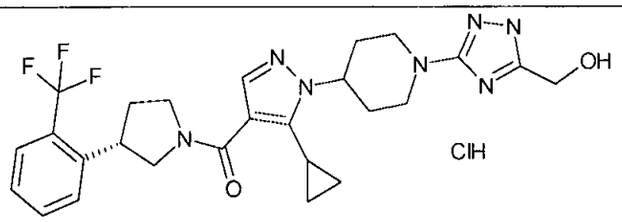
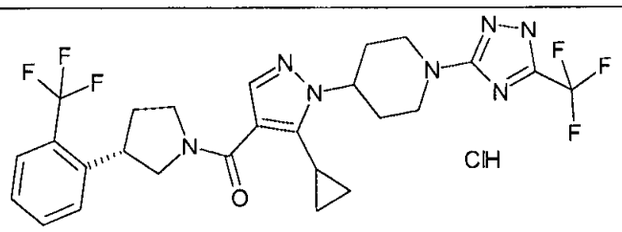
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CUADRO 1-29

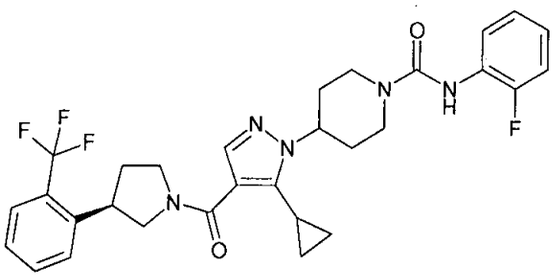
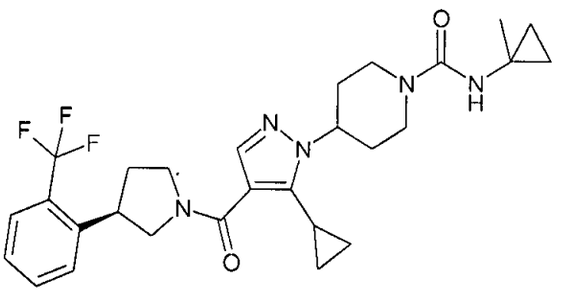
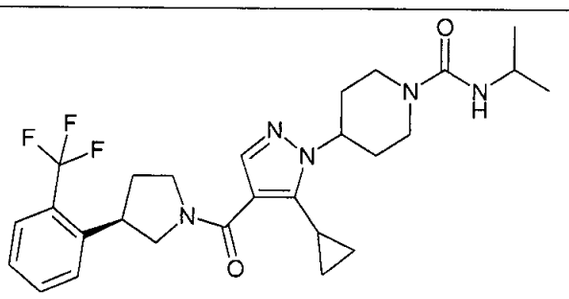
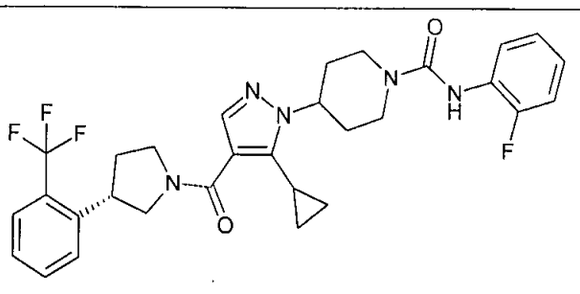
Ej. No.	Fórmula estructural	RMN
113		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.71-0.87 (2H; m); 1.03-1.18 (2H; m); 1.71-2.47 (7H; m); 3.00-3.18 (2H; m); 3.42-4.17 (7H; m); 4.56-4.75 (1H; m); 6.85-6.97 (2H; m); 7.32-7.71 (5H; m); 7.92-8.00 (2H; m)
114		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.87 (2H; m); 1.02-1.19 (2H; m); 1.74-2.50 (7H; m); 2.81-3.19 (2H; m); 3.44-4.14 (7H; m); 4.48-4.80 (1H; m); 7.07-7.85 (9H; m)
115		^{1}H-RMN (400MHz; DMSO-D6) δ: 0.59-0.77 (2H; m); 0.92-1.08 (2H; m); 1.87-2.36 (7H; m); 3.08-3.94 (9H; m); 4.60-4.81 (1H; m); 6.16-6.29 (1H; m); 7.38-7.80 (6H; m); 12.25(1H; bs)
116		^{1}H-RMN (300MHz; DMSO-D6) δΠ 0.62-0.73 (2H; m); 0.96-1.04 (2H; m); 1.87-2.33 (7H; m); 3.18-3.32 (3H; m); 3.44-3.91 (4H; m); 3.97-4.10 (2H; m); 4.66-4.80 (1H; m); 7.41-7.60 (2H; m); 7.63-7.78 (4H; m); 12.6 (1H; brs)

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CUADRO 1-30

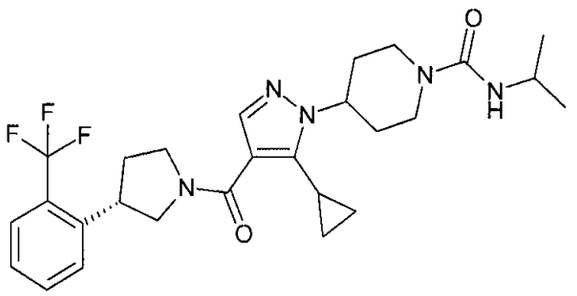
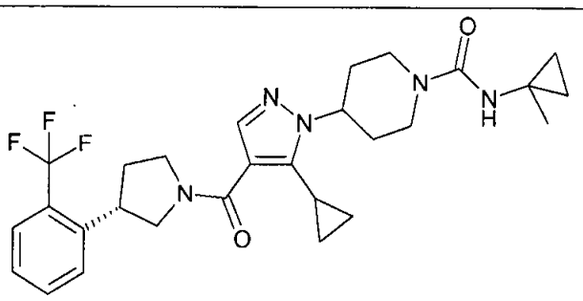
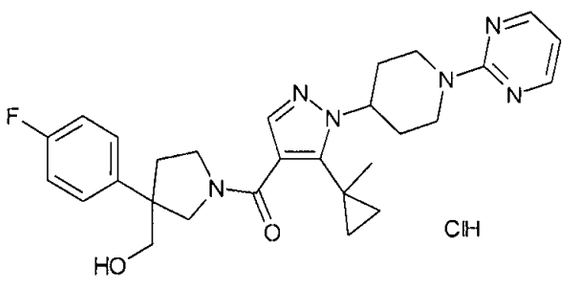
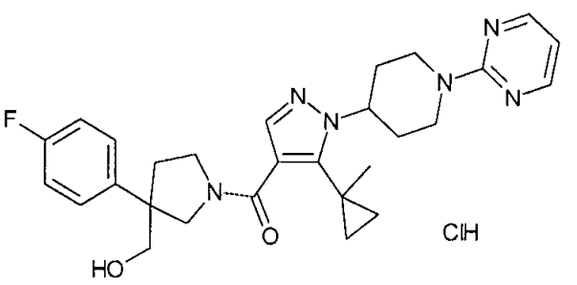
Ej. No.	Fórmula estructural	RMN
117		^{1}H-RMN (400MHz; DMSO-D6) δ: 0.59-0.77 (2H; m); 0.93-1.08(2H; m); 1.88-2.39 (10H; m); 3.21-4.12 (11H; m); 4.64-4.84 (1H; m); 7.41-7.80 (5H; m)
118		^{1}H-RMN (400MHz; DMSO-D6) δ: 0.60-0.75 (2H; m); 0.89-1.09 (6H; m); 1.86-2.36 (8H; m); 3.11-4.11 (11H; m); 4.61-4.82 (1H; m); 7.41-7.80 (5H; m)
119		^{1}H-RMN (400MHz; DMSO-D6) δ: 0.60-0.76 (2H; m); 0.92-1.06 (2H; m); 1.88-2.38 (8H; m); 3.15-4.15 (10H; m); 4.42-4.53 (2H; m); 4.63-4.82 (1H; m); 7.39-7.79 (6H; m)
120		^{1}H-RMN (400MHz; DMSO-D6) δ: 0.58-0.77 (2H; m); 0.92-1.06 (2H; m); 1.85-2.41 (7H; m); 3.11-4.10 (9H; m); 4.31-5.07 (2H; m); 7.41-7.79 (5H; m); 13.3-13.5 (1H; m)

CUADRO 1-31

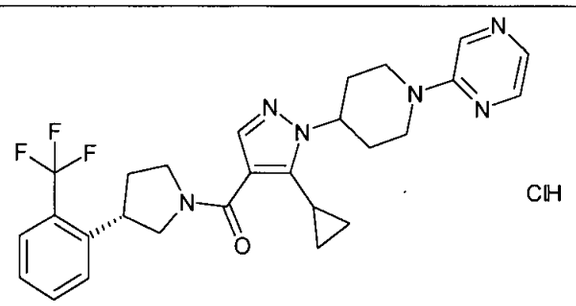
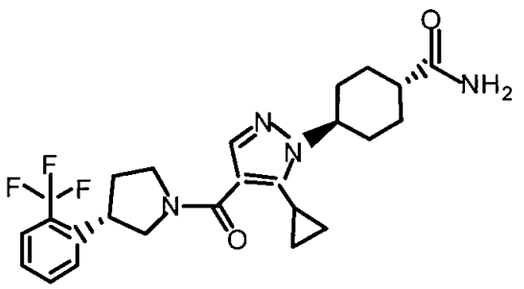
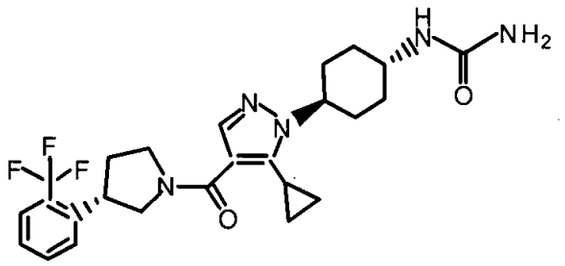
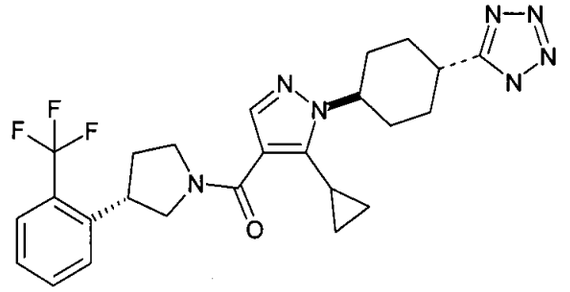
Ej. No.	Fórmula estructural	RMN
121		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.72-0.87 (2H; m); 1.05-1.15 (2H; m); 1.49-2.48 (7H; m); 3.05-3.22 (2H; m); 3.40-4.14 (5H; m); 4.20-4.36 (2H; m); 4.52-4.73 (1H; m); 6.60-6.71 (1H; m); 6.94-7.16 (3H; m); 7.33-7.72 (5H; m); 8.04-8.14 1H; m)
122		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.57-0.66 (2H; m); 0.66-0.84 (4H; m); 1.01-1.13 (2H; m); 1.32-1.45 (3H; m); 1.55-2.48 (7H; m); 2.81-3.00 (2H; m); 3.41-4.15 (5H; m); 4.44-4.63 (2H; m); 4.85-4.96 (1H; m); 7.33-7.71 (6H; m)
123		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.71-0.82 (2H; m); 1.02-1.13 (2H; m); 1.13-1.22 (6H; m);1.55-2.47 (8H; m); 2.84-3.01 (2H; m); 3.41-4.34 (9H; m); 4.45-4.63 (1H; m); 7.30-7.71 (6H; m)
124		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.72-0.87 (2H; m); 1.04-1.17 (2H; m); 1.53-2.46 (7H; m); 3.05-3.21 (2H; m); 3.42-4.11 (5H; m); 4.20-4.35 (2H; m); 4.55-4.71 (1H; m); 6.62-6.70 (1H; m); 6.93-7.16 (3H; m); 7.33-7.72 (5H; m); 8.04-8.14 (1H; m)

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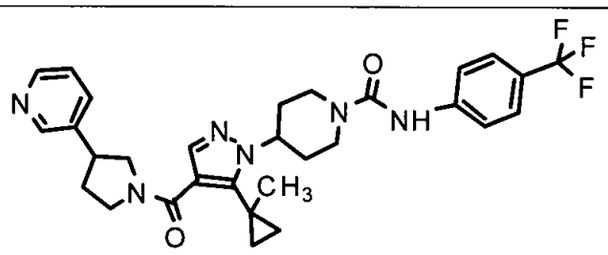
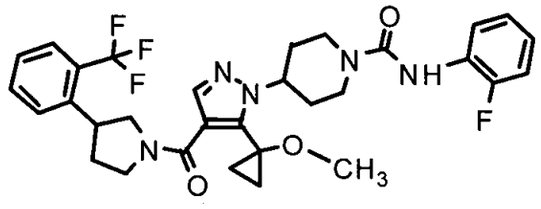
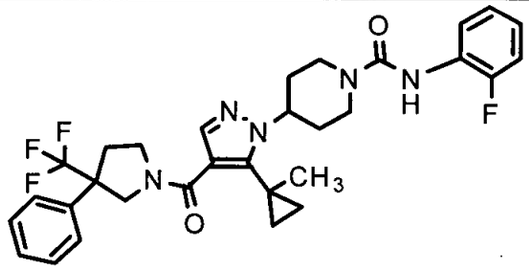
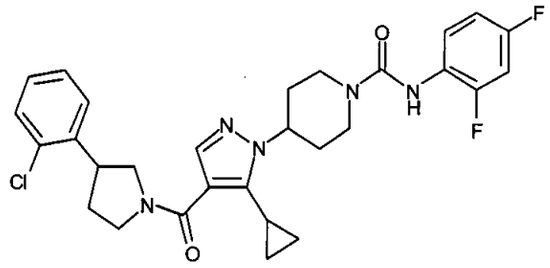
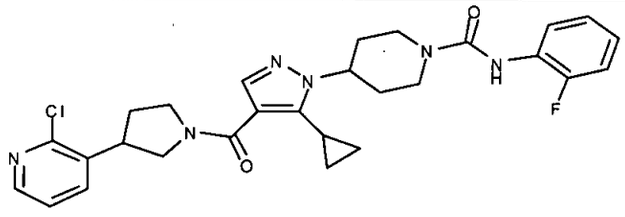
CUADRO 1-32

Ej. No.	Fórmula estructural	RMN
125		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.84 (2H; m); 1.03-1.13 (2H; m); 1.13-1.21 (6H; m); 1.55-2.47 (8H; m); 2.84-3.01 (2H; m); 3.41-4.31 (9H; m); 4.45-4.63 (1H; m); 7.33-7.72 (6H; m)
126		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.58-0.66 (2H; m); 0.66-0.83 (4H; m); 1.02-1.11 (2H; m); 1.36-1.43 (3H; m); 1.53-2.46 (7H; m); 2.83-2.99 (2H; m); 3.41-4.15 (5H; m); 4.45-4.61 (2H; m); 4.85-4.92 (1H; m); 7.32-7.72 (6H; m)
127		^{1}H-RMN (400MHz; DMSO-D6) δ: 0.56-0.86 (4H; m); 1.32-1.43 (3H; m); 1.85-2.12 (6H; m); 2.28-2.39 (1H; m); 3.09-3.26 (2H; m); 3.31-4.94 (6H; m); 4.74-4.91 (3H; m); 6.30 (1H; bs); 6.69-6.75 (1H; m); 7.07-7.37 (4H; m); 7.53-7.62 (1H; m); 8.40-8.50 (2H; m)
128		^{1}H-RMN (400MHz; DMSO-D6) δ: 0.56-0.88 (4H; m); 1.32-1.48 (3H; m); 1.85-2.12 (6H; m); 2.28-2.39 (1H; m); 3.09-3.24 (2H; m); 3.30-4.95 (6H; m); 4.73-4.93 (3H; m); 5.81 (1H; bs); 6.64-6.73 (1H; m); 7.06-7.40 (4H; m); 7.50-7.67 (1H; m); 8.39-8.49 (2H; m)

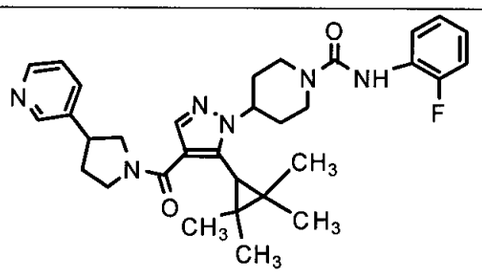
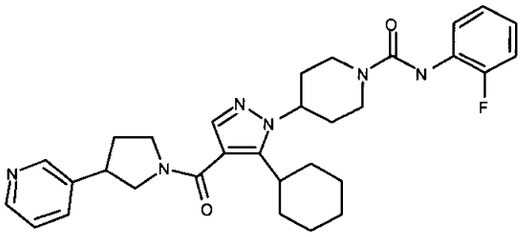
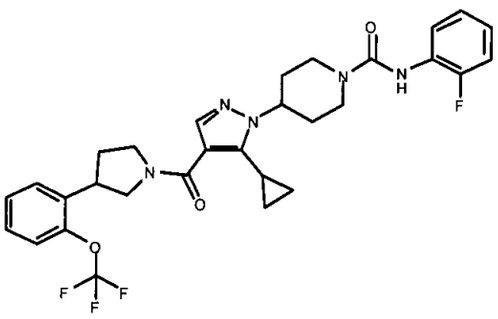
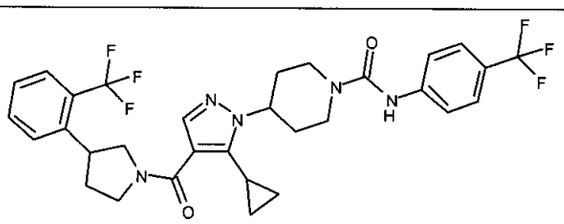
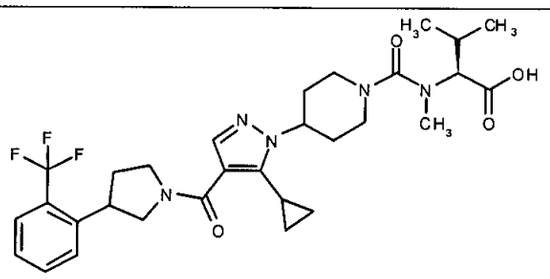
CUADRO 1-33

Ej. No.	Fórmula estructural	RMN
129		^{1}H-RMN (400MHz; DMSO-d6) δ: 0.66-0.69 (2H; m); 0.99-1.01 (2H; m); 1.91-2.33 (7H; m); 3.11-3.14 (2H; m); 3.46-3.89 (5H; m); 4.49-4.52 (2H; m); 4.75-4.77 (1H; m); 7.48-7.74 (6H; m); 7.85-7.90 (1H; m); 8.17 (1H; brs); 8.43-8.45 (1H; m)
130		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.65-0.79 (2H; m); 0.94-1.10 (2H; m); 1.63-2.44 (12H; m); 3.38-4.10 (5H; m); 4.32-4.51 (1H; m); 5.33 (1H; br); 5.51 (1H; br); 7.27-7.70 (5H; m)
131		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.62-0.82 (2H; m); 0.95-1.10 (2H; m); 1.23-1.39 (2H; m); 1.65-2.45 (8H; m); 3.40-4.10 (6H; m); 4.26-4.60 (4H; m); 7.27-7.71 (6H; m)
132		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.67-0.79 (2H; m); 0.84-0.92 (2H; m); 1.06-1.15 (2H; m); 1.22-1.35 (3H; m); 1.73-2.49 (8H; m); 3.05-3.19 (1H; m); 3.39-3.55 (1H; m); 3.61-4.17 (3H; m); 4.46-4.61 (1H; m); 7.33-7.71 (5H; m)

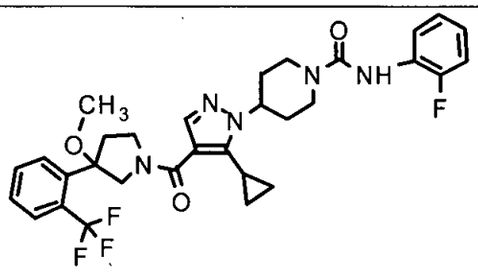
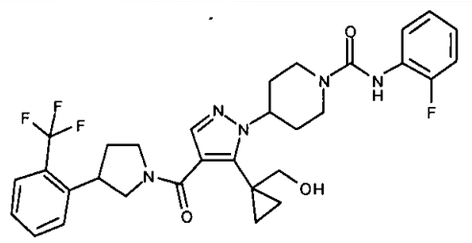
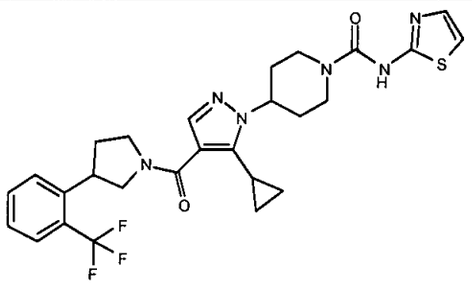
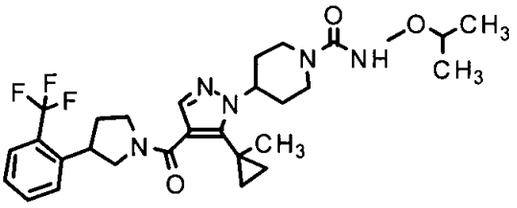
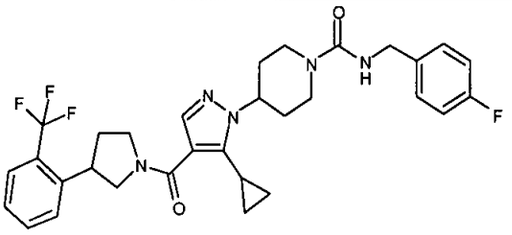
CUADRO 1-34

Ej. No.	Fórmula estructural	RMN
133		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.71-0.95 (4H; m); 1.38-1.47 (3H; m); 1.61-1.88 (2H; m); 1.99-2.29 (3H; m); 2.34-2.50 (1H; m); 2.94-3.12 (2H; m); 3.36-4.18 (5H; m); 4.25-4.40 (2H; m); 4.54-4.72 (1H; m); 6.99-7.33 (2H; m); 7.44-7.65 (6H; m); 8.44-8.61 (2H; m)
134		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.89-1.05 (2H; m); 1.22-1.34 (2H; m); 1.94-2.44 (6H; m); 3.05-3.21 (2H; m); 3.28-3.39 (3H; m); 3.42-4.11 (5H; m); 4.20-4.35 (2H; m); 4.77-4.93 (1H; m); 6.62-6.71 (1H; m); 6.93-7.18 (3H; m); 7.32-7.72 (5H; m); 8.05-8.14 (1H; m)
135		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.57-0.95 (4H; m); 1.34-1.54 (3H; m); 1.83-2.08 (2H; m); 2.18-2.41 (2H; m); 2.45-2.61 (1H; m); 2.73-2.92 (1H; m); 3.02-3.24 (2H; m); 3.51-4.86 (7H; m); 6.60-6.78 (1H; m); 6.93-7.18 (3H; m); 7.20-7.46 (5H; m); 7.46-7.57 (1H; m); 8.01-8.15 (1H; m)
136		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.71-0.81 (2H; m); 1.00-1.14 (2H; m); 1.71-1.85 (1H; m); 1.93-2.43 (6H; m); 3.05-3.19 (2H; m); 3.40-4.10 (5H; m); 4.20-4.33 (2H; m); 4.55-4.69 (1H; m); 6.48-6.57 (1H; m); 6.81-6.92 (2H; m); 7.17-7.45 (4H; m); 7.50-7.60 (1H; m); 7.94-8.03 (1H; m)
137		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.83 (2H; m); 1.01-1.14 (2H; m); 1.75-1.86 (1H; m); 1.94-2.36 (6H; m); 2.37-2.49 (1H; m); 3.07-3.20 (2H; m); 3.40-4.14 (4H; m); 4.22-4.34 (2H; m); 4.57-4.71 (1H; m); 6.61-

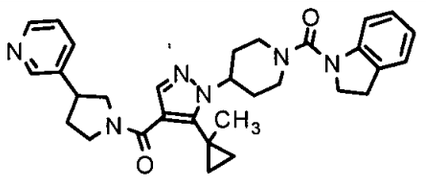
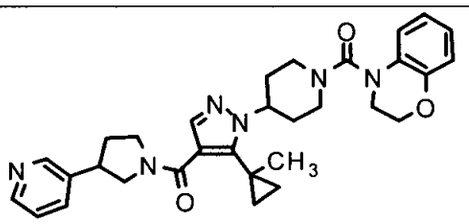
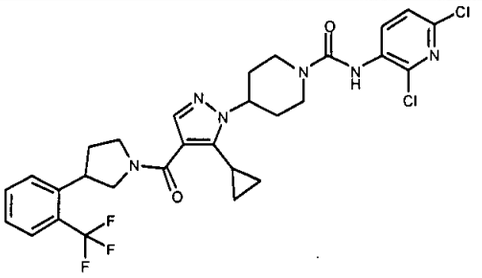
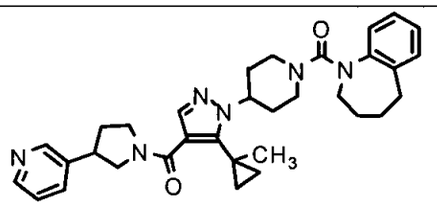
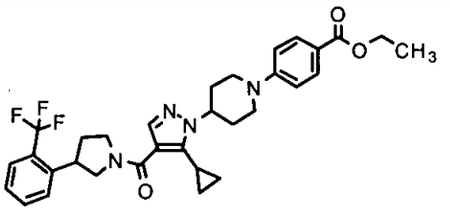
CUADRO 1-35

Ej. No.	Fórmula estructural	RMN
138		^{1}H-RMN ($CDCl_3$) δ: 0.94 (6H; s); 1.33 (6H; s); 2.03-2.11 (4H; m); 2.36-2.39 (2H; m); 3.07-3.09 (2H; m); 3.37-3.76 (4H; m); 3.89-3.96 (1H; m); 4.28-4.32 (4H; m); 6.65 (1H; s); 7.01-7.08 (3H; m); 7.24-7.32 (1H; m); 7.53-7.63 (2H; m); 8.07-8.09 (1H; m); 8.53-8.57 (2H; m)
139		^{1}H-RMN (300MHz; $CDCl_3$) δ: 1.25-1.48 (3H; m); 1.69-2.48 (13H; m); 2.85-3.19 (3H; m); 3.33-4.41 (8H; m); 6.59-6.69 (1H; m); 6.89-7.14 (3H; m); 7.23-7.36 (1H; m); 7.43-7.68 (2H; m); 8.05 (1H; t; J = 8.1 Hz); 8.44-8.59 (2H; m)
140		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.67-0.83 (2H; m); 1.01-1.15 (2H; m); 1.72-1.86 (1H; m); 1.92-2.43 (6H; m); 3.03-3.20 (2H; m); 3.36-4.11 (5H; m); 4.20-4.34 (2H; m); 4.55-4.71 (1H; m); 6.66 (1H; br s); 6.93-7.16 (3H; m); 7.20-7.42 (4H; m); 7.48-7.63 (1H; m); 8.03-8.14 (1H; m)
141		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.66-0.80 (2H; m); 1.00-1.12 (2H; m); 1.58-1.82 (3H; m); 1.97-2.23 (3H; m); 2.27-2.47 (1H; m); 2.90-3.06 (2H; m); 3.40-4.11 (5H; m); 4.24-4.41 (2H; m); 4.46-4.62 (1H; m); 7.32-7.73 (10H; m)
142		^{1}H-RMN (400MHz; DMSO-D_6) δ: 0.57-0.74 (2H; m); 0.81-1.03 (8H; m); 1.79-2.36 (8H; m); 2.82-2.90 (8H; m); 3.44-3.92 (9H; m); 4.50-4.70 (1H; s); 7.42-7.53 (2H; m); 7.55-7.61 (1H; m); 7.66-7.78 (2H; m)

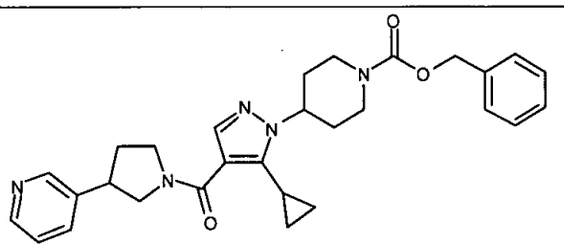
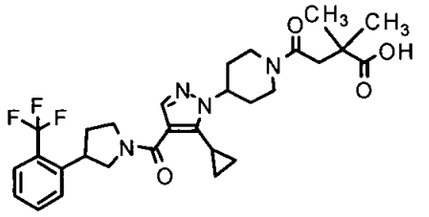
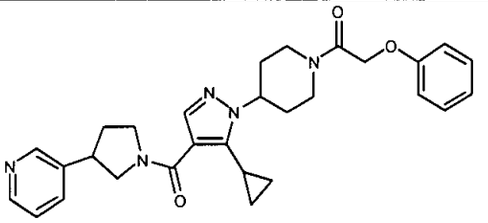
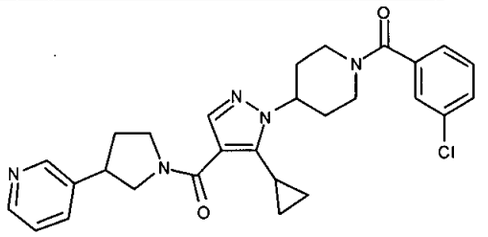
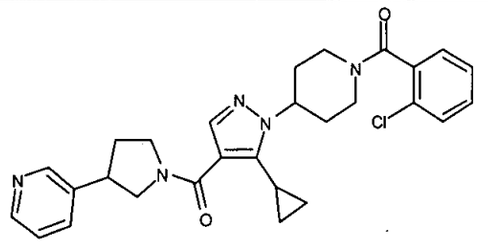
CUADRO 1-36

Ej. No.	Fórmula estructural	RMN
143		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.62-0.84 (2H; m); 0.91-1.17 (2H; m); 1.67-1.88 (1H; m); 1.91-2.08 (2H; m); 2.14-2.42 (2.5H; m); 2.43-2.56 (0.5H; m); 2.57-2.72 (1H; m); 2.88-3.21 (5H; m); 3.45-3.61 (0.6H; m); 3.64-3.91 (2H; m); 3.98-4.13 (1H; m); 4.19-4.36 (2.4H; m); 4.53-4.72 (1H; m); 6.63-6.79 (1H; m); 6.89-7.18 (3H; m); 7.40-7.64 (4H; m); 7.75-7.93 (1H; m); 8.00-8.13 (1H; m)
144		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.97 (2H; m); 0.97-1.35 (2H; m); 1.85-2.54 (6H; m); 2.87-3.21 (2H; m); 3.21-4.14 (7H; m); 4.16-4.46 (2H; m); 4.51-4.79 (1H; m); 5.98-6.35 (1H; m); 6.56-6.78 (1H; m); 6.85-7.20 (3H; m); 7.20-7.79 (5H; m); 7.95-8.16 (1H; m)
145		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.84 (2H; m); 1.01-1.16 (2H; m); 1.68-1.85 (1H; m); 1.88-2.46 (6H; m); 3.02-3.19 (2H; m); 3.40-4.11 (5H; m); 4.24-4.41 (2H; m); 4.53-4.71 (1H; m); 6.82-6.91 (1H; m); 7.30-7.72 (7H; m)
146		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.71-0.99 (4H; m); 1.15-1.31 (6H; m); 1.35-1.52 (3H; m); 1.73-1.98 (2H; m); 1.98-2.47 (4H; m); 2.86-3.08 (2H; m); 3.42-4.11 (6H; m); 4.12-4.31 (2H; m); 4.53-4.72 (1H; m); 7.08-7.21 (1H; m); 7.30-7.40 (1H; m); 7.41-7.61 (3H; m); 7.61-7.74 (1H; m)
147		^{1}H-RMN (300MHz; $CDCl_3$) δ: 0.64-0.81 (2H; m); 0.96-1.13 (2H; m); 1.55-1.93 (3H; m); 1.95-2.44 (4H; m); 2.84-3.02 (2H; m); 3.36-4.22 (7H; m); 4.30-4.41 (2H; m); 4.43-4.62 (1H; m); 4.83-4.99 (1H; m); 6.91-7.05 (2H; m); 7.17-7.71 (7H; m)

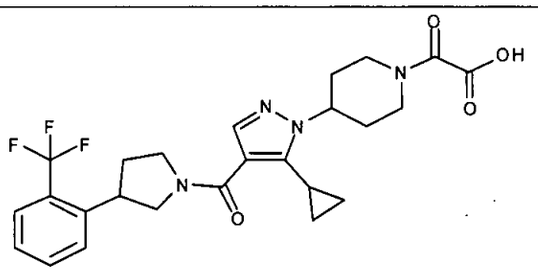
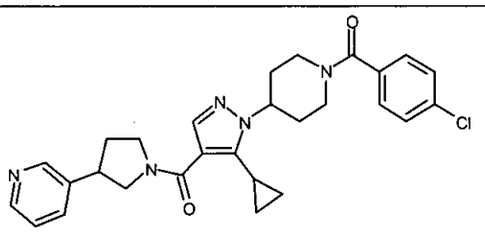
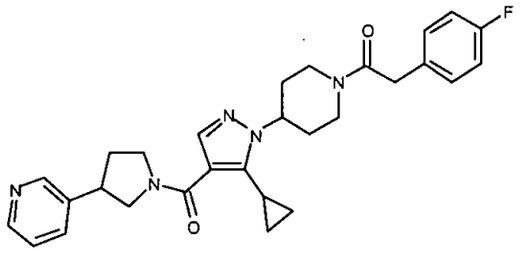
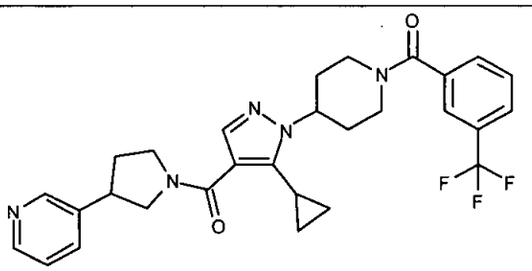
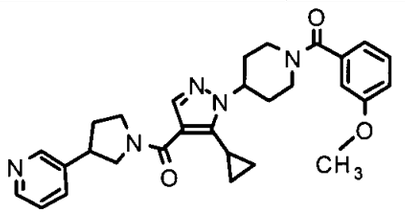
CUADRO 1-37

Ej. No.	Fórmula estructural	RMN
148		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.73-0.84 (2H; m); 0.85-0.96 (2H; m); 1.45 (3H; s); 1.84-1.97 (2H; m); 2.01-2.20 (1H; m); 2.26-2.49 (3H; m); 2.97-3.12 (4H; m); 3.37-4.19 (9H; m); 4.61-4.75 (1H; m); 6.86-6.95 (1H; m); 7.08-7.22 (3H; m); 7.25-7.33 (1H; m); 7.48-7.65 (2H; m); 8.46-8.63 (2H; m)
149		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.82 (2H; m); 0.82-0.96 (2H; m); 1.42 (3H; s); 1.79-1.97 (2H; m); 1.98-2.19 (4H; m); 2.93-3.08 (2H; m); 3.33-3.82 (5.5H; m); 3.84-4.01 (1H; m); 4.04-4.23 (2.5H; m); 4.26-4.40 (2H; m); 4.55-4.73 (1H; m); 6.81-6.97 (3H; m); 7.11-7.22 (1H; m); 7.23-7.35 (1H; m); 7.46-7.67 (2H; m); 8.44-8.62 (2H; m)
150		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.85 (2H; m); 1.02-1.18 (2H; m); 1.72-1.87 (1H; m); 1.94-2.46 (6H; m); 3.08-3.26 (2H; m); 3.41-4.11 (5H; m); 4.18-4.33 (2H; m); 4.57-4.75 (1H; m); 6.97-7.07 (1H; m); 7.23-7.61 (5H; m); 7.64-7.72 (1H; m); 8.53-8.60 (1H; m)
151		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.61-0.89 (4H; m); 1.36 (3H; s); 1.55-1.83 (6H; m); 1.89-2.17 (3H; m); 2.32-2.47 (1H; m); 2.59-2.82 (4H; m); 3.33-4.18 (9H; m); 4.38-4.52 (1H; m); 7.03-7.14 (2H; m); 7.16-7.32 (3H; m); 7.43-7.64 (2H; m); 8.44-8.61 (2H; m)
152		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.71-0.85 (2H; m); 1.03-1.16 (2H; m); 1.33-1.42 (3H; m); 1.73-1.88 (1H; m); 1.93-2.22 (3H; m); 2.25-2.45 (3H; m); 2.96-3.13 (2H; m); 3.41-4.11 (7H; m); 4.28-4.39 (2H; m); 4.52-4.71 (1H; m); 6.85-6.96 (2H; m); 7.32-7.40 (1H; m); 7.41-7.61 (3H; m); 7.63-

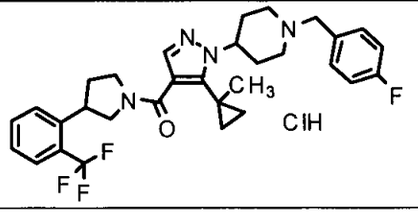
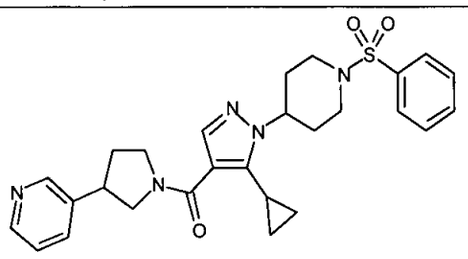
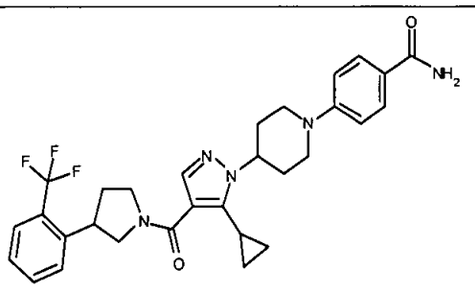
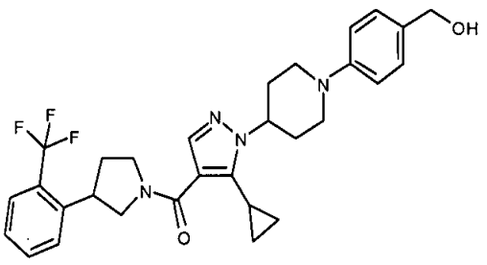
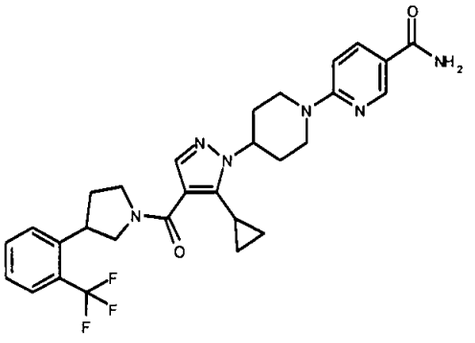
CUADRO 1-38

Ej. No.	Fórmula estructural	RMN
153		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.65-0.79 (2H; m); 1.00-1.09 (2H; m); 1.70-1.97 (3H; m); 2.00-2.26 (3H; m); 2.31-2.47 (1H; m); 2.86-3.05 (2H; m); 3.35-3.53 (1.5H; m); 3.56-3.77 (2H; m); 3.84-3.94 (1H; m); 4.08-4.16 (0.5H; m); 4.25-4.61 (3H; m); 5.14 (2H; s); 7.23-7.40 (6H; m); 7.49-7.61 (2H; m); 8.47-8.57 (2H; m)
154		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.61-0.86 (2H; m); 0.98-1.18 (2H; m); 1.23-1.41 (6H; m); 1.67-1.86 (1H; m); 1.87-2.47 (6H; m); 2.52-2.88 (3H; m); 3.06-3.32 (1H; m); 3.35-4.15 (6H; m); 4.49-4.85 (2H; m); 7.28-7.73 (5H; m)
155		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.62-0.83 (2H; m); 0.97-1.14 (2H; m); 1.66-2.50 (8H; m); 2.78-2.95 (1H; m); 3.16-3.34 (1H; m); 3.37-3.54 (1H; m); 3.57-3.79 (2H; m); 3.83-3.97 (1H; m); 4.09-4.29 (1H; m); 4.54-4.80 (4H; m); 6.89-7.04 (3H; m); 7.21-7.38 (3H; m); 7.48-7.68 (2H; m); 8.42-8.70 (2H; m)
156		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.65-0.82 (2H; m); 1.00-1.13 (2H; m); 1.67-2.30 (9H; m); 2.32-2.51 (1H; m); 2.72-3.34 (2H; m); 3.36-4.03 (4H; m); 4.56-4.99 (1H; m); 7.20-7.46 (5H; m); 7.49-7.65 (2H; m); 8.42-8.62 (2H; m)
157		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.64-0.85 (2H; m); 0.98-1.13 (2H; m); 1.57-1.92 (3H; m); 1.96-2.50 (5H; m); 2.90-3.54 (3H; m); 3.56-3.81 (3H; m); 3.83-3.98 (1H; m); 4.53-4.73 (1H; m); 4.85-5.04 (1H; m); 7.21-7.47 (5H; m); 7.49-7.65 (2H; m); 8.45-8.62 (2H; m)

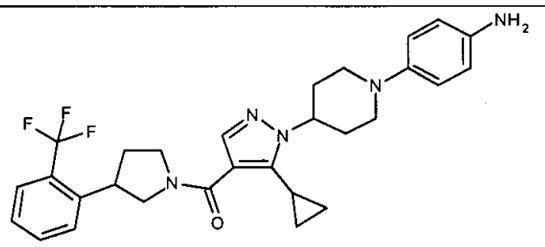
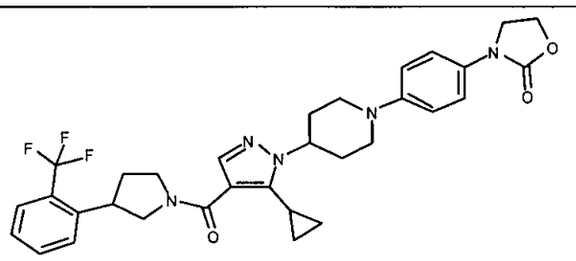
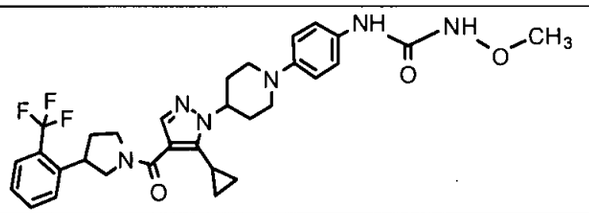
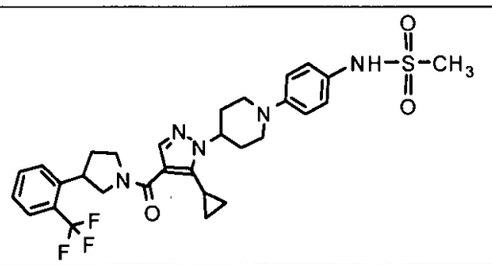
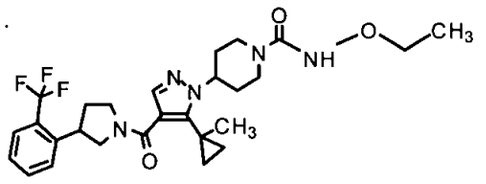
CUADRO 1-39

Ej. No.	Fórmula estructural	RMN
158		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.62-1.19 (4H; m); 1.62-2.53 (7H; m); 2.70-2.92 (1H; m); 3.08-3.29 (1H; m); 3.33-4.21 (6H; m); 4.51-4.75 (2H; m); 7.31-7.62 (4H; m); 7.63-7.73 (1H; m)
159		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.64-0.82 (2H; m); 0.98-1.12 (2H; m); 1.65-2.32 (9H; m); 2.34-2.50 (1H; m); 3.08 (2H; brs); 3.34-4.00 (4H; m); 4.56-4.95 (1H; m); 7.23-7.32 (1H; m); 7.35-7.44 (4H; m); 7.48-7.65 (2H; m); 8.45-8.61 (2H; m)
160		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.59-0.83 (2H; m); 0.95-1.14 (2H; m); 1.62-2.20 (6H; m); 2.30-2.50 (1H; m); 2.69-2.91 (1H; m); 3.06-3.27 (1H; m); 3.33-4.20 (6H; m); 3.73 (2H; s); 4.50-4.66 (1H; m); 4.71-4.85 (1H; m); 6.93-7.10 (2H; m); 7.15-7.34 (3H; m); 7.45-7.64 (2H; m); 8.41-8.62 (2H; m)
161		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.65-0.81 (2H; m); 0.99-1.13 (2H; m); 1.72-2.50 (9H; m); 2.85-3.33 (2H; m); 3.35-3.78 (3H; m); 3.81-4.96 (3H; m); 7.22-7.33 (1H; m); 7.47-7.77 (6H; m); 8.44-8.63 (2H; m)
162		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.64-0.82 (2H; m); 1.00-1.12 (2H; m); 1.71-2.32 (8H; m); 2.33-2.51 (1H; m); 2.85-3.28 (2H; m); 3.32-4.05 (5H; m); 3.83 (3H; s); 4.57-4.99 (1H; m); 6.90-7.04 (3H; m); 7.24-7.38 (2H; m); 7.50-7.69 (2H;

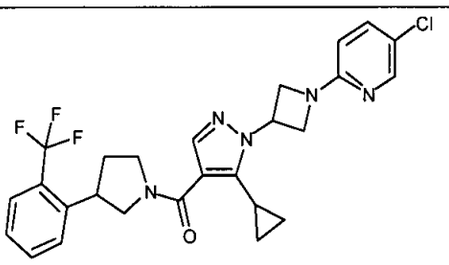
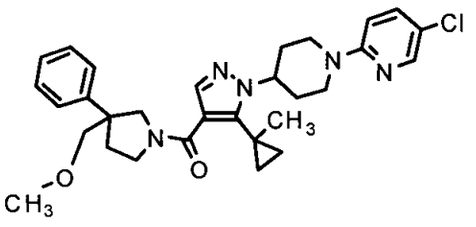
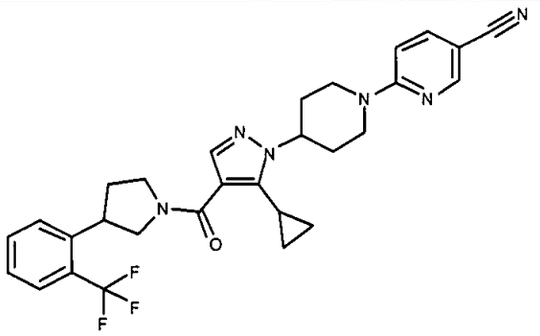
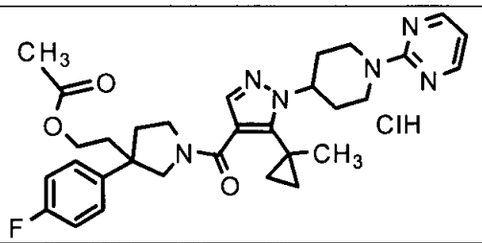
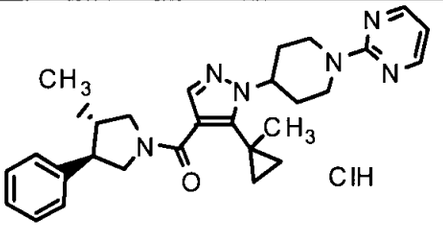
CUADRO 1-40

Ej. No.	Fórmula estructural	RMN
163		^{1}H-RMN (400MHz; DMSO-D_6) δ: 0.68-0.86 (4H; m); 1.29-1.38 (3H; m); 1.99-2.17 (2H; m); 2.18-2.66 (5H; m); 3.14-3.32 (2H; m); 3.39-4.50 (8H; m); 4.68-4.83 (1H; m); 7.30-7.40 (2H; m); 7.43-7.53 (1H; m); 7.60-7.82 (6H; m); 10.55-10.76 (1H; m)
164		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.59-0.74 (2H; m); 0.93-1.04 (2H; m); 1.61-1.73 (1H; m); 1.88-2.16 (3H; m); 2.25-2.59 (5H; m); 3.34-3.76 (3.5H; m); 3.83-4.01 (3H; m); 4.08-4.15 (0.5H; m); 4.27-4.39 (1H; m); 7.23-7.31 (1H; m); 7.49-7.67 (5H; m); 7.79-7.84 (2H; m); 8.46-8.58 (2H; m)
165		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.67-0.86 (2H; m); 1.00-1.19 (2H; m); 1.73-1.88 (1H; m); 1.92-2.21 (3H; m); 2.24-2.47 (3H; m); 2.92-3.12 (2H; m); 3.40-4.12 (7H; m); 4.51-4.69 (1H; m); 5.74 (2H; br s); 6.87-6.99 (2H; m); 7.31-7.40 (1H; m); 7.41-7.61 (3H; m); 7.63-7.78 (3H; m)
166		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.85 (2H; m); 1.01-1.16 (2H; m); 1.51-1.67 (1H; m); 1.75-1.89 (1H; m); 1.91-2.23 (3H; m); 2.26-2.49 (3H; m); 2.83-3.00 (2H; m); 3.40-4.12 (7H; m); 4.44-4.68 (3H; m); 6.88-7.04 (2H; m); 7.23-7.31 (2H; m); 7.32-7.40 (1H; m); 7.41-7.62 (3H; m); 7.63-7.72 (1H; m)
167		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.73-0.86 (2H; m); 1.06-1.12 (2H; m); 1.76-1.88 (1H; m); 1.94-2.08 (2H; m); 2.11-2.44 (5H; m); 3.05-3.19 (2H; m); 3.42-3.51 (0.5H; m); 3.59-4.10 (3.5H; m); 4.56-4.78 (3H; m); 5.40-5.94 (2H; brs); 6.67-6.74 (1H; m); 7.12-7.22 (1H; m); 7.31-7.40 (1H; m); 7.41-7.60 (2H; m); 7.64-7.73 (1H; m); 7.91-7.99 (1H; m); 8.56-8.63 (1H; m)

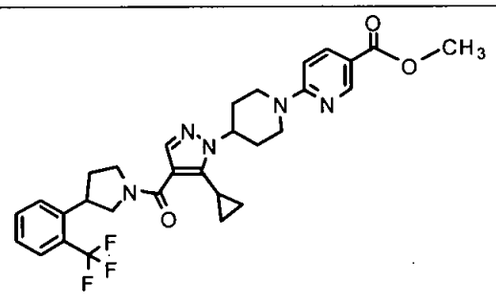
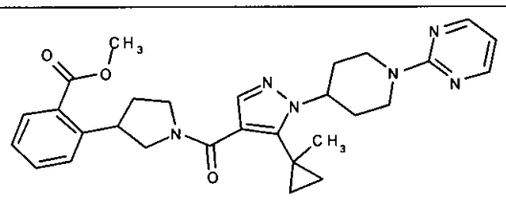
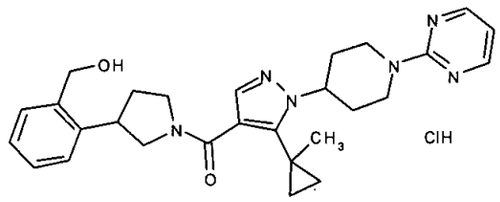
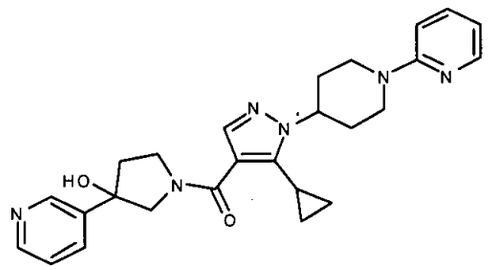
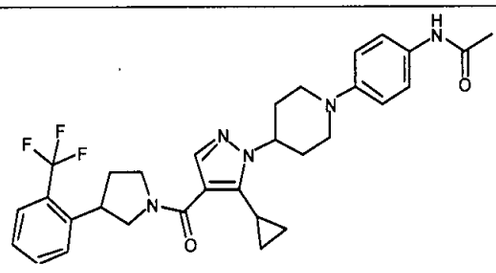
CUADRO 1-41

Ej. No.	Fórmula estructural	RMN
168		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.71-0.85 (2H; m); 1.02-1.14 (2H; m); 1.73-1.88 (1H; m); 1.90-2.22 (3H; m); 2.27-2.51 (3H; m); 2.71-2.88 (2H; m); 3.35-4.11 (9H; m); 4.38-4.56 (1H; m); 6.60-6.71 (2H; m); 6.78-6.91 (2H; m); 7.31-7.40 (1H; m); 7.41-7.62 (3H; m); 7.63-7.71 (1H; m)
169		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.71-0.88 (2H; m); 1.02-1.16 (2H; m); 1.73-1.88 (1H; m); 1.91-2.19 (3H; m); 2.27-2.50 (3H; m); 2.81-3.00 (2H; m); 3.40-4.17 (9H; m); 4.39-4.63 (3H; m); 6.92-7.04 (2H; m); 7.31-7.72 (7H; m)
170		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.86 (2H; m); 1.01-1.16 (2H; m); 1.72-1.88 (1H; m); 1.91-2.23 (3H; m); 2.26-2.51 (3H; m); 2.76-2.98 (2H; m); 3.42-4.11 (10H; m); 4.42-4.62 (1H; m); 6.89-7.00 (2H; m); 7.16 (1H; s); 7.31-7.73 (8H; m)
171		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.86 (2H; m); 1.00-1.16 (2H; m); 1.72-1.88 (1H; m); 1.92-2.23 (3H; m); 2.26-2.48 (3H; m); 2.84-3.02 (5H; m); 3.38-4.12 (7H; m); 4.45-4.65 (1H; m); 6.25-6.38 (1H; m); 6.88-6.99 (2H; m); 7.11-7.22 (2H; m); 7.32-7.40 (1H; m); 7.41-7.62 (3H; m); 7.63-7.71 (1H; m)
172		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-1.01 (4H; m); 1.16-1.35 (3H; m); 1.35-1.53 (3H; m); 1.71-1.97 (2H; m); 1.97-2.49 (4H; m); 2.86-3.09 (2H; m); 3.41-4.31 (9H; m); 4.53-4.75 (1H; m); 7.17-7.30 (1H; m); 7.30-7.40 (1H; m); 7.41-7.60 (3H; m); 7.61-7.74 (1H; m)

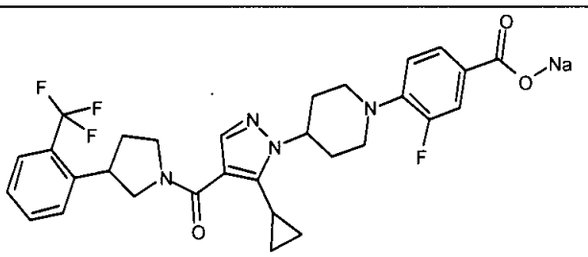
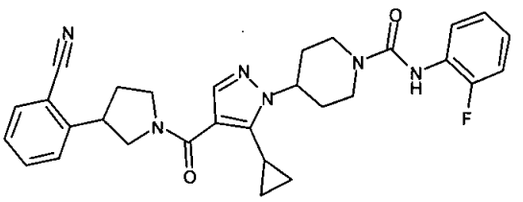
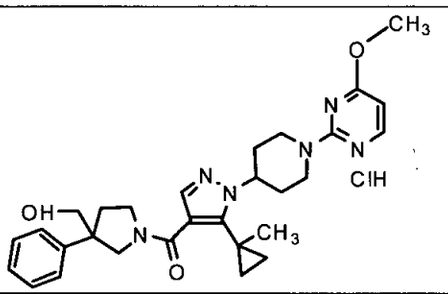
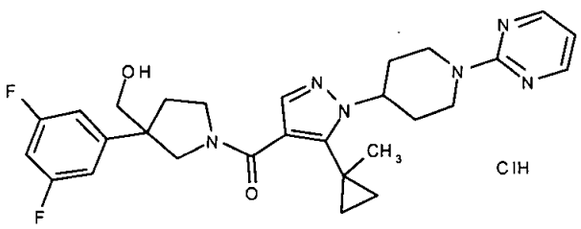
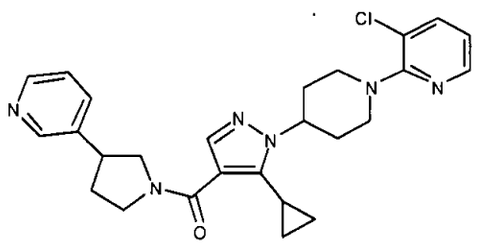
CUADRO 1-42

Ej. No.	Fórmula estructural	RMN
173		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.61-0.87 (2H; m); 1.00-1.19 (2H; m); 1.57-1.87 (1H; m); 1.93-2.25 (1H; m); 2.25-2.48 (1H; m); 3.31-4.15 (5H; m); 4.35-4.59 (4H; m); 5.44-5.66 (1H; m); 6.26-6.40 (1H; m); 7.30-7.76 (6H; m); 8.02-8.17 (1H; m)
174		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.69-0.93 (4H; m); 1.41-1.52 (3H; m); 1.83-2.01 (2H; m); 2.13-2.51 (4H; m); 2.97-3.11 (2H; m); 3.16-4.12 (9H; m); 4.41-4.54 (2H; m); 4.65-4.78 (1H; m); 6.62-6.71 (1H; m); 7.12-7.55 (7H; m); 8.10-8.16 (1H; m)
175		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.72-0.85 (2H; m); 1.04-1.16 (2H; m); 1.73-1.88 (1H; m); 1.94-2.09 (2H; m); 2.10-2.45 (5H; m); 3.07-3.22 (2H; m); 3.42-3.51 (0.5H; m); 3.57-4.10 (3.5H; m); 4.52-4.80 (3H; m); 6.62-6.71 (1H; m); 7.32-7.41 (1H; m); 7.41-7.72 (5H; m); 8.38-8.45 (1H; m)
176		^{1}H-RMN (400MHz; DMSO-D_6) δ: 0.46-0.86 (4H; m); 1.07-1.24 (2H; m); 1.27-1.41 (3H; m); 1.73-2.07 (7H; m); 2.15-2.30 (2H; m); 3.06-4.08 (8H; m); 4.72-4.88 (3H; m); 6.66-6.74 (1H; m); 7.08-7.61 (5H; m); 8.38-8.48 (2H; m)
177		^{1}H-RMN (400MHz; DMSO-D_6) δ: 0.70-0.97 (7H; m); 1.35-1.42 (3H; m); 1.86-2.03 (4H; m); 2.25-2.46 (1H; m); 2.84-2.95 (1H; m); 3.07-3.24 (3H; m); 3.39-3.57 (1H; m); 3.67-3.77 (1H; m); 3.81-3.94 (1H; m); 4.75-4.88 (3H; m); 6.64-6.72 (1H; m); 7.20-7.41 (5H; m); 7.53-7.61 (1H; m); 8.39-8.44 (2H; m)

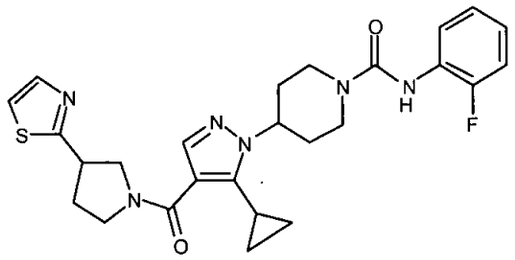
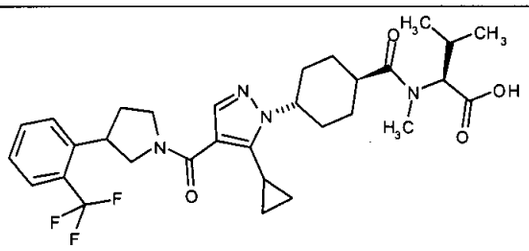
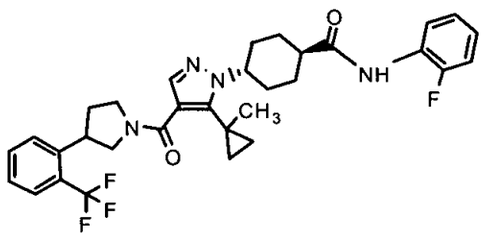
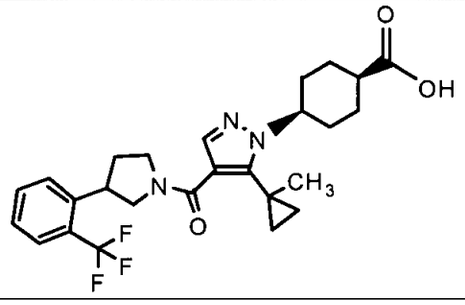
CUADRO 1-43

Ej. No.	Fórmula estructural	RMN
178		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.74-0.86 (2H; m); 1.05-1.15 (2H; m); 1.76-1.88 (1H; m); 1.93-2.09 (3H; m); 2.11-2.46 (4H; m); 3.04-3.19 (2H; m); 3.43-3.51 (0.5H; m); 3.59-4.09 (3.5H; m); 3.84-3.91 (3H; s); 4.58-4.78 (3H; m); 6.61-6.71 (1H; m); 7.32-7.61 (3.5H; m); 7.63-7.71 (1H; m); 7.98-8.08 (1.5H; m); 8.77-8.83 (1H; m)
179		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.77-0.98 (4H; m); 1.44-1.53 (3H; m); 1.86-2.46 (6H; m); 2.99-3.15 (2H; m); 3.45-4.06 (7H; m); 4.18-4.41 (1H; m); 4.68-4.85 (1H; m); 4.94-5.09 (2H; m); 6.48-6.55 (1H; m); 7.26-7.56 (4H; m); 7.82-7.92 (1H; m); 8.31-8.37 (2H; m)
180		^{1}H-RMN (400MHz; DMSO-D_6) δ: 0.67-0.91 (4H; m); 1.29-1.44 (3H; m); 1.74-2.34 (7H; m); 3.02-4.18 (7H; m); 4.47-4.69 (2H; m); 4.77-4.91 (3H; m); 6.60-6.71 (1H; m); 7.14-7.69 (5H; m); 8.34-8.46 (2H; m)
181		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.77 (2H; m); 0.99-1.15 (2H; m); 1.75-1.89 (1H; m); 1.92-2.05 (2H; m); 2.18-2.53 (4H; m); 2.96-3.09 (2H; m); 3.68-3.85 (2H; m); 3.87-4.04 (2H; m); 4.44-4.56 (2H; m); 4.58-4.72 (1H; m); 6.58-6.67 (1H; m); 6.68-6.76 (1H; m); 7.29-7.39 (1H; m); 7.45-7.53 (2H; m); 7.75-7.88 (1H; m); 8.17-8.23 (1H; m); 8.54-8.62 (1H; m); 8.69-8.83 (1H; m)
182		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.83 (2H; m); 1.01-1.15 (2H; m); 1.69-1.88 (1H; m); 1.90-2.21 (6H; m); 2.26-2.50 (3H; m); 2.77-3.00 (2H; m); 3.41-4.11 (7H; m); 4.40-4.62 (1H; m); 6.85-6.97 (2H; m); 7.31-7.71 (7H; m)

CUADRO 1-44

Ej. No.	Fórmula estructural	RMN
183		^{1}H-RMN (400MHz; DMSO-D_6) δ: 0.60-0.75 (2H; m); 0.94-1.06 (2H; m); 1.88-2.34 (7H; m); 2.79-2.98 (2H,m); 3.44-3.93 (7H; m); 4.50-4.68 (1H; m); 6.89-7.03 (1H; m); 7.43-7.80 (7H; m)
184		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.70-0.86 (2H; m); 1.05-1.16 (2H; m); 1.77-1.88 (1H; m); 1.94-2.53 (6H; m); 3.06-3.22 (2H; m); 3.45-4.16 (5H; m); 4.21-4.35 (2H; m); 4.57-4.73 (1H; m); 6.67 (1H; s); 6.95-7.17 (3H; m); 7.35-7.73 (5H; m); 8.05-8.13 (1H; m)
185		^{1}H-RMN (400MHz; DMSO-D_6) δ: 0.58-0.88 (4H; m); 1.29-1.44 (3H; m); 1.94-2.21 (5H; m); 2.28-2.41 (1H; m); 3.27-3.93 (8H; m); 3.95-4.05 (3H; m); 4.58-4.97 (3H; m); 5.42-6.26 (1H; m); 6.37-6.50 (1H; m); 7.14-7.41 (5H; m); 7.53-7.68 (1H; m); 8.11-8.23 (1H; m)
186		^{1}H-RMN (400MHz; DMSO-D_6) δ: 0.55-0.85 (4H; m); 1.32-1.41 (3H; m); 1.84-2.40 (7H; m); 3.06-3.23 (2H; m); 3.29-3.90 (5H; m); 4.72-4.88 (3H; m); 4.89-5.35 (2H; m); 6.66-6.72 (1H; m); 6.91-7.64 (4H; m); 8.39-8.44 (2H; m)
187		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.68-0.85 (2H; m); 1.01-1.13 (2H; m); 1.57-1.88 (2H; m); 1.93-2.20 (1H; m); 2.33-2.56 (3H; m); 2.94-3.07 (2H; m); 3.35-3.82 (4H; m); 3.86-4.21 (4H; m); 4.52-4.66 (1H; m); 6.82-6.88 (1H; m); 7.24-32 (3H; m); 7.55-7.64 (3H; m); 8.15-8.22 (1H; m); 8.47-8.61 (1H; m)

CUADRO 1-45

Ej. No.	Fórmula estructural	RMN
188		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.67-0.78 (2H; m); 0.96-1.11 (2H; m); 1.71-1.85 (1H; m); 1.92-2.09 (3H; m); 2.16-2.57 (4H; m); 3.04-3.21 (2H; m); 3.55-4.00 (4H; m); 4.19-4.34 (2H; m); 4.54-4.68 (1H; m); 6.61-6.70 (1H; m); 6.91-7.15 (3H; m); 7.23-7.31 (1H; m); 7.51-7.58 (1H; m); 7.67-7.76 (1H; m); 8.03-8.12 (1H; m)
189		^{1}H-RMN (400MHz; DMSO-D_6) δ: 0.53-0.69 (2H; m); 0.71-0.88 (2H; m); 0.91-1.11 (6H; m); 1.43-2.39 (10H; m); 2.62-2.82 (2H; m); 2.92-3.06 (3H; m); 3.42-3.92 (6H; m); 4.10-4.74 (2H; m); 7.39-7.59 (2H; m); 7.63-7.81 (2H; m)
190		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.73-0.97 (4H; m); 1.36-1.51 (3H; m); 1.77-1.95 (2H; m); 1.97-2.26 (7H; m); 2.29-2.49 (2H; m); 3.47-4.11 (5H; m); 4.46-4.64 (1H; m); 7.00-7.20 (3H; m); 7.32-7.72 (6H; m); 8.29-8.42 (1H; m)
191		^{1}H-RMN (400MHz; $CDCl_3$) δ: 0.73-0.97 (4H; m); 1.38-1.49 (3H; m); 1.60-1.76 (1H; m); 1.77-1.90 (2H; m); 1.93-2.18 (2H; m); 2.19-2.56 (5H; m); 2.70-2.81 (1H; m); 3.47-4.09 (5H; m); 4.42-4.61 (1H; m); 7.31-7.72 (5H; m)

La presente invención será concretamente descrita ahora mediante los ejemplos de formulación siguientes, los cuales no deben ser interpretados como restrictivos de la misma.

Ejemplo de formulación 1 (producción de cápsula)

1) compuesto del ejemplo 1	30 mg
2) celulosa cristalina	10 mg
3) lactosa	19 mg
4) estearato de magnesio	1 mg

1), 2), 3) y 4) fueron mezclados y rellenados en una cápsula de gelatina.

Ejemplo de formulación 2 (producción de tableta)

1) compuesto del ejemplo 1	30 g
2) lactosa	50 g
3) almidón de maíz	15 g
4) carboximetilcelulosa de calcio	44 g
5) estearato de magnesio	1 g

La cantidad total de 1), 2), 3) y 30 g de 4) fue amasada con agua, secada bajo presión reducida y cribada. El polvo cribado fue mezclado con 14 g de 4) y 1 g de 5), y formado en tableta con una máquina de fabricar tabletas. De esta manera, se obtienen 1000 tabletas que contienen 30 mg por tableta del compuesto del ejemplo 1.

De la misma manera como en el ejemplo de formulación 1 o el ejemplo de formulación 2 indicados precedentemente, los compuestos de los ejemplos 2 a 191 también pueden ser utilizados para producir cápsulas o tabletas.

Ejemplo experimental 1

Actividad inhibitoria de la acción de HSD-1 (hidroxiesteroide deshidrogenasa 1) *in vitro*

La actividad inhibitoria de la acción de HSD-1 fue determinada por cuantificación de la inhibición de conversión de cortisona a cortisol por un sistema SPA (ensayo de proximidad de centelleo) y usando, como fuente de enzima, HSD-1 de humano (más adelante en la presente HSD-1 recombinante) expresado usando sistema de baculovirus. Los reactivos (100 µl) fueron agregados a una placa de 96 pocillos (Opti-plates™-96 (Packard)) a una concentración final ilustrada más adelante y la reacción se realizó a temperatura ambiente durante 90 a 120 min. Como una mezcla de reacción, fueron agregados 5-100 ng/pocillo HSD-1 recombinante, 500 µM de NADPH y 10 nM ^{3}H de cortisona (American Radiolabeled Chemicals Inc., 50 Ci/mmol) fueron disueltos en PBS que contiene 0.1% de BSA (Sigma), y la substancia de prueba fue 2 µl de una solución compuesta (disuelta en DMSO). Después de la reacción, 50 µl de PBS (conteniendo 0.1% de BSA (Sigma)) conteniendo 0.2 µg de anticuerpo monoclonal de ratón anticortisol (East Coast Biologics), 500 µg de anticuerpos anti-ratón unidos a PVT SPA en cuentas (Amersham Biosciences) y 133 µM de carbenoxolona (Sigma) fueron agregados a la mezcla de reacción para detener la reacción. Después de realizada la reacción, la mezcla fue incubada a temperatura ambiente durante por lo menos 2 h, y la radioactividad fue medida con Topcount (Packard). Como el control, fueron usados los valores de pocillo con agregados de 2 µl de DMSO en vez de la sustancia de prueba (0% de inhibición) y, como control positivo, se utilizaron los valores de los pocillos a los que se agregó carbenoxolona (concentración final 100 µM) en vez de la

sustancia de prueba (100% de inhibición).

La inhibición (%) de la sustancia de prueba fue calculada de ((valor de control - valor sustancia de prueba)/(valor de control - valor de control positivo)) x 100 (%). El valor de IC_{50} fue calculado de la relación de inhibición de dos puntos que atraviesan el 50% de inhibición. Los resultados obtenidos se ilustran en el cuadro 2-1 al cuadro 2-3 a continuación.

CUADRO 2-1

Ej. No.	hHSD1(IC_{50}(nM))	Ej. No.	hHSD1(IC_{50}(nM))
2	++	41	++
3	++	42	++
4	++	43	++
6	++	44	++
7	++	45	++
8	++	47	++
9	++	48	++
10	++	49	++
11	++	50	++
12	++	51	++
13	++	52	++
14	++	53	++
15	++	54	++
16	++	55	++
17	++	56	++
18	++	57	++
19	++	58	++
20	++	59	++
21	++	60	++
22	++	61	++
23	++	63	++
24	++	64	++
25	++	65	++
26	++	66	++
27	++	67	++
28	++	68	++
29	++	69	++
30	++	71	++
31	++	72	++
32	++	73	++
33	++	74	++
34	++	75	++
35	++	76	++
36	++	77	++
37	++	78	++
39	++	79	++
40	++	80	++

CUADRO 2-2

Ej. No.	hHSD1(IC_{50}(nM))	Ej. No.	hHSD1(IC_{50}(nM))
83	++	130	++
84	++	131	++
85	++	132	++
87	++	133	++
88	++	134	++
89	++	135	++
90	++	136	++
91	++	137	++
93	++	138	++
94	++	139	++
95	++	140	++
96	++	141	++
97	++	142	++
99	++	145	++
100	++	146	++
103	++	147	++
105	++	148	++
106	++	149	++
107	++	150	++
108	++	151	++
109	++	154	++
110	++	155	++
111	++	156	++
112	++	157	++
113	++	158	++
114	++	165	++
115	++	166	++
116	++	167	++
117	++	168	++
118	++	169	++
119	++	170	++
120	++	171	++
124	++	172	++
125	++	173	++
126	++	174	++
128	++	175	++
129	++	176	++

CUADRO 2-3

Ej. No.	hHSD1(IC_{50}(nM))	Ej. No.	hHSD1(IC_{50}(nM))
177	++	185	++
178	++	186	++
179	++	187	++
180	++	189	++
182	++	190	++
183	++	191	++
184	++		

En los cuadros anteriores, ++ significa valores IC_{50} que no superan 30 nM.

APLICACION INDUSTRIAL

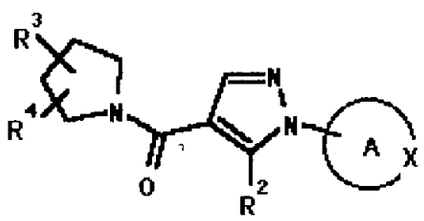
Los compuestos heterocíclicos de la presente invención poseen una acción inhibitoria de HSD1 superior y son útiles como agente para profilaxis o tratamiento de enfermedades metabólicas tales como diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión, hígado graso y lo similar.

Esta solicitud está basada en las solicitudes de patente Nos. 2005-168901 y 2006-027097 registradas en Japón, y 60/692,039 y 60/772,734 registradas en E.U.A, sus contenidos son incorporados a la presente como referencia.

NOVEDAD DE LA INVENCION

REIVINDICACIONES

1. Un compuesto representado por la fórmula siguiente [1']:



[1']

en donde: el anillo A es (1) un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o (2) un grupo cicloalquilo, dicho anillo A es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes R^1, dicho sustituyente R^1 es 1) un átomo de hidrógeno, 2) $-CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es (a) un átomo de hidrógeno, (b) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, c) un grupo carboxilo, d) un grupo de alquilo C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y e) un grupo alcoxilo de C_{1-6}), (c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), (d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de

halógeno, c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), d) -$NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv): (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo oxo, y (iv) un grupo alcoxilo de C_{1-6}), e) un grupo alcoxilo de C_{1-6}, y f) un grupo carboxilo), (e) -$S(=O)_2$-R^9 en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, (f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), (g) un grupo alcoxilo de C_{1-6}, o (h) un grupo heterocíclico monocíclico no saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o (i) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o un grupo heterocíclico que es un anillo fusionado de dicho heterociclo y

un anillo de carbono (ambos grupos heterocíclicos indicados son opcionalmente sustituidos con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i): a) un átomo de halógeno, b) un grupo hidroxilo, c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), d) un grupo carboxilo, e) un grupo -CO-alquilo de C_{1-6}, f) -CO-$NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, g) un grupo oxo, h) -$NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y i) un grupo alcoxilo de C_{1-6}), 3) -$COOR^{10}$ en donde R^{10} es (a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al d): a) un grupo hidroxilo, b) -$NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, c) un grupo alcoxilo de C_{1-6}, y d) un grupo arilo), o (b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), 4) -COR^{11} en donde R^{11} es (a) un

grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) a la h): a) un átomo de halógeno, b) un grupo hidroxilo, c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, d) $-CO-NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, e) un grupo alcoxilo de C_{1-6}, f) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo alcoxilo de C_{1-6}, y (iv) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), g) un grupo carboxilo, y h) un grupo ariloxilo), (b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b): a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), (c) un grupo heterocíclico monocíclico saturado que contiene

nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), (d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes (1) a (3): (1) un átomo de halógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), y (3) un grupo alcoxilo de C_{1-6}), o (e) un grupo carboxilo, 5) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes (a) a (d): (a) un grupo carboxilo, (b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno), (c)-CO-$NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y (d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes))), 6) un grupo cicloalquilo, 7) -$S(=O)_2$-R^{12} en donde R^{12} es un grupo alquilo

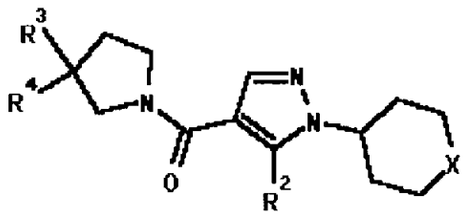
de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), 8) $-C(=NCN)-R^{13}$ en donde R^{13} es un grupo alquilo de C_{1-6}, 9) $-C(=NCN)NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, 10) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (f): (a) un grupo carboxilo, (b) un átomo de halógeno, (c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, y c) un grupo alcoxilo de C_{1-6}), (d) $-NR^{38}R^{39}$ en donde R^{38} y R^{39} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, $-CO-NR^{40}R^{41}$ en donde R^{40} y R^{41} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo alcoxilo de C_{1-6}, o R^{40} y R^{41} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o $-S(=O)_2-R^{42}$ en donde R^{42} es un grupo alquilo de C_{1-6}, o R^{38} y R^{39} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterociclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más grupos oxo), (e) $-CO-NR^{43}R^{44}$ en donde R^{43} y R^{44} son iguales o diferentes y cada

uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{43} y R^{44} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y (f) un grupo -COO-alquilo de C_{1-6}), o 11) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes (a) a (h): (a) un grupo carboxilo, (b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un átomo de halógeno, b) un grupo hidroxilo, y c) un grupo alcoxilo de C_{1-6}), (c) un grupo cicloalquilo, (d) un átomo de halógeno, (e) -CO-$NR^{45}R^{46}$ en donde R^{45} y R^{46} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{45} y R^{46} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, (f) un grupo -COO-alquilo de C_{1-6}, (g) un grupo ciano, y (h) un grupo alcoxilo de C_{1-6}); -X- es (1) -N(R^1)- en donde R^1 es igual al definido anteriormente, o (2) -C(R^7R^8)- en donde R^7 y R^8 son iguales o diferentes y cada uno es 1) un átomo de hidrógeno, 2) -$NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o -CO-$NR^{36}R^{37}$ en donde R^{36} y R^{37} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{36} y R^{37} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno), o R^{16} y R^{17} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, 3) -$CONR^{18}R^{19}$ en donde R^{18} y R^{19} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más

grupos carboxilo), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un átomo de halógeno, y (b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o R^{18} y R^{19} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, 4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros, o 5) un grupo carboxilo; R^2 es (1) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un grupo hidroxilo, y (b) un grupo alcoxilo de C_{1-6}), y 2) un grupo alcoxilo de C_{1-6}); y R^3 y R^4 son iguales o diferentes y cada uno es (1) un átomo de hidrógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) átomo halógeno, 2) un grupo hidroxilo, 3) un grupo alcoxilo de C_{1-6}, y 4) un grupo -OCO-alquilo de C_{1-6}), (3) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente 1) a 6): 1) un átomo de halógeno, 2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un átomo de halógeno, (b) un grupo hidroxilo, y (c) un grupo alcoxilo de C_{1-6}), 3) un grupo alcoxilo de C_{1-6} (dicho grupo alcoxilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), 4) un grupo carboxilo, 5) un grupo -COO-alquilo de C_{1-6}, y 6) un grupo ciano), (4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6

miembros (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un átomo de halógeno, y 2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), (5) un grupo hidroxilo, o (6) un grupo alcoxilo de C_{1-6}], o una sal del mismo.

2. Un compuesto representado por la fórmula siguiente [1]:



[1]

en donde: -X- es (1) -N(R^1)- en donde R^1 es 1) un átomo de hidrógeno, 2) -CONR^{5}R^6 en donde R^5 y R^6 son iguales o diferentes y cada uno es (a) un átomo de hidrógeno, (b) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, c) un grupo carboxilo, d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y e) un grupo alcoxilo de C_{1-6}), (c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), (d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), d) -NR^{20}R^{21} en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21}

opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv): (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo oxo, y (iv) un grupo alcoxilo de C_{1-6}), e) un grupo alcoxilo de C_{1-6}, y f) un grupo carboxilo), (e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, (f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), (g) un grupo alcoxilo de C_{1-6}, o (h) un grupo heterocíclico monocíclico no saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), ó (i) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o un grupo heterocíclico que es un anillo fusionado de dicho heterociclo y un anillo de carbono (ambos grupos heterocíclicos mencionados son sustituidos opcionalmente por uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i): a) un átomo de halógeno, b) un grupo hidroxilo, c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), d) un grupo

carboxilo, e) un grupo -CO-alquilo de C_{1-6}, f) -CO-$NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, g) un grupo oxo, h) -$NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y i) un grupo alcoxilo de C_{1-6}), 3) -$COOR^{10}$ en donde R^{10} es (a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al d): a) un grupo hidroxilo, b) -$NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, c) un grupo alcoxilo de C_{1-6}, y d) un grupo arilo), ó (b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), 4) -COR^{11} en donde R^{11} es (a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) a la h): a) un átomo de halógeno, b) un grupo hidroxilo, c) -$NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo -$S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos,

un grupo heterocíclico monocíclico saturado que contiene nitrógeno, d) -CO-$NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, e) un grupo alcoxilo de C_{1-6}, f) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo alcoxilo de C_{1-6}, y (iv) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), g) un grupo carboxilo, y h) un grupo ariloxilo), (b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b): a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), (c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), (d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) a (3): (1) un átomo de halógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente

sustituido con uno o más átomos halógenos iguales o diferentes), y (3) un grupo alcoxilo de C_{1-6}), o (e) un grupo carboxilo, 5) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (d): (a) un grupo carboxilo, (b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, -CO-$NR^{32}R^{33}$ iguales o diferentes en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno), (c) -CO-NR34R^{35} en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y (d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes))), 6) un grupo cicloalquilo, 7) $-S(=O)_2-R^{12}$ en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), 8) $-C(=NCN)-R^{13}$ en donde R^{13} es un grupo alquilo

de C_{1-6}, 9) $-C(=NCN)NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, 10) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (f): (a) un grupo carboxilo, (b) un átomo de halógeno, (c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, y c) un grupo alcoxilo de C_{1-6}), (d) $-NR^{38}R^{39}$ en donde R^{38} y R^{39} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, $-CO-NR^{40}R^{41}$ en donde R^{40} y R^{41} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo alcoxilo de C_{1-6}, o R^{40} y R^{41} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o $-S(=O)_2-R^{42}$ en donde R^{42} es un grupo alquilo de C_{1-6}, o R^{38} y R^{39} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más grupos oxo), (e) $-CO-NR^{43}R^{44}$ en donde R^{43} y R^{44} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{43} y R^{44} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y (f) un grupo -COO-alquilo de C_{1-6}), o 11) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (h): (a) un grupo carboxilo, (b)

un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un átomo de halógeno, b) un grupo hidroxilo, y c) un grupo alcoxilo de C_{1-6}), (c) un grupo cicloalquilo, (d) un átomo de halógeno, (e) -CO-$NR^{45}R^{46}$ en donde R^{45} y R^{46} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{45} y R^{46} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, (f) un grupo -COO-alquilo de C_{1-6}, (g) un grupo ciano, y (h) un grupo alcoxilo de C_{1-6})), o (2) -C(R^7R^8)- en donde R^7 y R^8 son iguales o diferentes y cada uno es 1) un átomo de hidrógeno, 2) -$NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o -CO-$NR^{36}R^{37}$ en donde R^{36} y R^{37} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{36} y R^{37} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, ó R^{16} y R^{17} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, 3) -$CONR^{18}R^{19}$ en donde R^{18} y R^{19} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más grupos carboxilo), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un átomo de halógeno, y (b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o R^{18} y R^{19} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, 4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6

miembros, o 5) un grupo carboxilo; R^2 es (1) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un grupo hidroxilo, y (b) un grupo alcoxilo de C_{1-6}), y 2) un grupo alcoxilo de C_{1-6}); y R^3 y R^4 son iguales o diferentes y cada uno es (1) un átomo de hidrógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un átomo de halógeno, 2) grupo hidroxilo, 3) un grupo alcoxilo de C_{1-6}, y 4) un grupo -OCO-alquilo de C_{1-6}), (3) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente 1) a 6): 1) un átomo de halógeno, 2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (a) un átomo de halógeno, (b) un grupo hidroxilo, y (c) un grupo alcoxilo de C_{1-6}), 3) un grupo alcoxilo de C_{1-6} (dicho grupo alcoxilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), 4) un grupo carboxilo, 5) un grupo -COO-alquilo de C_{1-6}, y 6) un grupo ciano), (4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un átomo de halógeno, y 2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), (5) un grupo hidroxilo, o (6) un grupo alcoxilo de C_{1-6}], o una sal del mismo.

3. El compuesto de conformidad con cualquiera de las

reivindicaciones 1 y 2, caracterizado además porque -X- es -C(R^7R^8)- en donde R^7 y R^8 son iguales a los definidos en la reivindicación 1, o una sal del mismo.

4. El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque R^8 es 1) -$NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{16} y R^{17} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, 2) -$CONR^{18}R^{19}$ en donde R^{18} y R^{19} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{18} y R^{19} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o 3) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros, o una sal del mismo.

5. El compuesto de conformidad con la reivindicación 1 o 2, caracterizado además porque -X- es -N(R^1)- en donde R^1 es igual al definido en la reivindicación 1, o una sal del mismo.

6. El compuesto de conformidad con cualquiera de las reivindicaciones 1, 2 y 5, caracterizado además porque R^1 es 1) un átomo de hidrógeno, 2) -$CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es (a) un átomo de hidrógeno, (b) un grupo arilo (dicho grupo arilo es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, c) un grupo carboxilo, d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}) y e) un grupo alcoxilo de C_{1-6}), (c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o

más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), (d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes (i) a (iv): (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo oxo, y (iv) un grupo alcoxilo de C_{1-6}), e) un grupo alcoxilo de C_{1-6}, y f) un grupo carboxilo), (e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, o (f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), o (g) un

grupo heterocíclico monocíclico no saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), ó (h) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i): a) un átomo de halógeno, b) un grupo hidroxilo, c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), d) un grupo carboxilo, e) un grupo -CO-alquilo de C_{1-6}, f) -CO-$NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, g) un grupo oxo, h) -$NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y i) un grupo alcoxilo de C_{1-6}) (con la condición que R^5 y R^6 no sean simultáneamente átomos de hidrógeno), 3) -$COOR^{10}$ en donde R^{10} es (a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al d): a) un grupo hidroxilo, b) -$NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, c) un grupo alcoxilo de C_{1-6}, y d) un grupo arilo), o (b) un

grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), 4) - COR^{11} en donde R^{11} es (a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) a la h): a) un átomo de halógeno, b) un grupo hidroxilo, c) -$NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo -$S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, d) -CO-$NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, e) un grupo alcoxilo de C_{1-6}, f) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo alcoxilo de C_{1-6}, y (iv) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), g) un grupo carboxilo, y h) un grupo ariloxilo), (b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b): a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más

átomos halógenos iguales o diferentes)), y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), ó (c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), (d) un grupo arilo (dicho grupo arilo es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) a (3): (1) un átomo de halógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), y (3) un grupo alcoxilo de C_{1-6}), ó (e) un grupo carboxilo, 5) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (d): (a) un grupo carboxilo, (b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C1-6), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno), (c) -CO-$NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y (d) un grupo arilo (dicho grupo arilo es

opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes))), 6) un grupo cicloalquilo, 7) $-S(=O)_2-R^{12}$ en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), 8) - $C(=NCN)-R^{13}$ en donde R^{13} es un grupo alquilo de C_{1-6}, 9) $-C(=NCN)NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, 10) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (f): (a) un grupo carboxilo, (b) un átomo de halógeno, (c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, y c) un grupo alcoxilo de C_{1-6}), (d) $-NR^{38}R^{39}$ en donde R^{38} y R^{39} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, $-CO-NR^{40}R^{41}$ en donde R^{40} y R^{41} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo alcoxilo de C_{1-6}, o R^{40} y R^{41} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o $-S(=O)_2-R^{42}$ en donde

R^{42} es un grupo alquilo de C_{1-6}, o R^{38} y R^{39} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más grupos oxo), (e) -CO-$NR^{43}R^{44}$ en donde R^{43} y R^{44} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{43} y R^{44} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y (f) un grupo -COO-alquilo de C_{1-6}), o 11) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterociclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (h): (a) un grupo carboxilo, (b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un átomo de halógeno, b) un grupo hidroxilo, y c) un grupo alcoxilo de C_{1-6}), (c) un grupo cicloalquilo, y (d) un átomo de halógeno, (e) -CO-$NR^{45}R^{46}$ en donde R^{45} y R^{46} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{45} y R^{46} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, (f) un grupo -COO-alquilo de C_{1-6}, (g) un grupo ciano, y (h) un grupo alcoxilo de C_{1-6}), o una sal del mismo.

7. El compuesto de conformidad con cualquiera de las reivindicaciones 1, 2 y 5, caracterizado además porque R^1 es 1) -$CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es (a) un átomo de hidrógeno, (b) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, c) un grupo carboxilo, d) un grupo alquilo de C_{1-6}

(dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y e) un grupo alcoxilo de C_{1-6}), (c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), (d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv): (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo oxo, y (iv) un grupo alcoxilo de C_{1-6}), e) un grupo alcoxilo de C_{1-6}, y f) un grupo carboxilo), (e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o

un grupo alquilo de C_{1-6}, o (f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), (g) un grupo alcoxilo de C_{1-6}, o (h) un grupo heterocíclico monocíclico no saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o (i) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i): a) un átomo de halógeno, b) un grupo hidroxilo, c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), d) un grupo carboxilo, e) un grupo -CO-alquilo de C_{1-6}, f) -CO-$NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, g) un grupo oxo, h) -$NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y i) un grupo alcoxilo de C_{1-6}) (con la condición que R^5 y R^6 no son cualquier combinación de sustituyentes seleccionada del grupo siguiente: (i) un átomo de hidrógeno, y (ii) un grupo alquilo de C_{1-6} sin sustituir), 2) -$COOR^{10}$ en donde R^{10} es (a) un grupo alquilo de C_{1-6} (dicho grupo

alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al d): a) un grupo hidroxilo, b) $-NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, c) un grupo alcoxilo de C_{1-6}, y d) un grupo arilo), o (b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), 3) $-COR^{11}$ en donde R^{11} es (a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al h): a) un átomo de halógeno, b) un grupo hidroxilo, c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, d) $-CO-NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, e) un grupo alcoxilo de C_{1-6}, f) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo alcoxilo de C_{1-6}, y (iv) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), g) un grupo carboxilo, y h) un

grupo ariloxilo), (b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b): a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más, átomos halógenos iguales o diferentes)), y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), o (c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), (d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) a (3): (1) un átomo de halógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), y (3) un grupo alcoxilo de C_{1-6}), o (e) un grupo carboxilo, 4) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (d): (a) un grupo carboxilo, (b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con

el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno), (c) -CO-$NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y (d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes))), 5) un grupo cicloalquilo, 6) -$S(=O)_2$-R^{12} en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más átomos halógenos iguales o diferentes), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), 7) -C(=NCN)-R^{13} en donde R^{13} es un grupo alquilo de C_{1-6}, 8) -C(=NCN)$NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o 9) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (g): (a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un átomo de halógeno, b) un grupo hidroxilo, y c) un grupo alcoxilo de C_{1-6}), (b) un grupo cicloalquilo, (c) un átomo de halógeno, (d) -CO-$NR^{45}R^{46}$ en donde R^{45} y R^{46} son

iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{45} y R^{46} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, (e) un grupo -COO-alquilo de C_{1-6}, (f) un grupo ciano, y (g) un grupo alcoxilo de C_{1-6}), o una sal del mismo.

8. El compuesto de de conformidad con cualquiera de las reivindicaciones 1, 2 y 5, caracterizado además porque R^1 es 1) $-CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es (a) un átomo de hidrógeno, (b) un grupo arilo (dicho grupo arilo es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, c) un grupo carboxilo, d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y e) un grupo alcoxilo de C_{1-6}), (c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), (d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de

hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv): (i) un átomo de halógeno, (ii) un grupo hidroxilo. (iii) un grupo oxo, y (iv) un grupo alcoxilo de C_{1-6}), e) un grupo alcoxilo de C_{1-6}, y f) un grupo carboxilo), (e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, o (f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, y b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), o (g) un grupo heterocíclico monocíclico no saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o (h) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i): a) un átomo de halógeno, b) un grupo hidroxilo, c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), d) un grupo carboxilo, e) un grupo -CO-alquilo de C_{1-6}, f) $-CO-NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o

diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, g) un grupo oxo, h) $-NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y i) un grupo alcoxilo de C_{1-6}) (con la condición que R^5 y R^6 no sean simultáneamente átomos de hidrógeno), 2) $-COOR^{10}$ en donde R^{10} es (a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al d): a) un grupo hidroxilo, b) $-NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, c) un grupo alcoxilo de C_{1-6}, y d) un grupo arilo), o (b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), 3) $-COR^{11}$ en donde R^{11} es (a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al h): a) un átomo de halógeno, b) un grupo hidroxilo, c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene

nitrógeno, d) -CO-$NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, e) un grupo alcoxilo de C_{1-6}, f) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo alcoxilo de C_{1-6}, y (iv) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), g) un grupo carboxilo, y h) un grupo ariloxilo), (b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b): a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), o (c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), (d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) a (3): (1) un átomo de halógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), y

(3) un grupo alcoxilo de C_{1-6}), o (e) un grupo carboxilo, 4) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (d): (a) un grupo carboxilo, (b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno), (c) -CO-$NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y (d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes))), 5) un grupo cicloalquilo, 6) -$S(=O)_2$-R^{12} en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más átomos halógenos iguales o diferentes), o un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), 7) -C(=NCN)-R^{13} en donde R^{13} es un grupo alquilo de C_{1-6}, 8) -C(=NCN)$NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un

grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o 9) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterociclico es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (g): (a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un átomo de halógeno, b) un grupo hidroxilo, y c) un grupo alcoxilo de C_{1-6}), (b) un grupo cicloalquilo, (c) un átomo de halógeno, (d) -CO-$NR^{45}R^{46}$ en donde R^{45} y R^{46} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{45} y R^{46} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, (e) un grupo -COO-alquilo de C_{1-6}, (f) un grupo ciano, y (g) un grupo alcoxilo de C_{1-6}), o una sal del mismo.

9. El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 8, caracterizado además porque R^2 es un grupo ciclopropilo o un grupo 1-metilciclopropilo, o una sal del mismo.

10. El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 9, caracterizado además porque R^3 y R^4 son iguales o diferentes y cada uno es (1) un átomo de hidrógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un átomo de halógeno, y 2) un grupo -OCO-alquilo de C_{1-6}), (3) un grupo arilo (dicho grupo arilo es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes 1) a 5): 1) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes

iguales o diferentes seleccionados del grupo siguiente: (a) un átomo de halógeno, y (b) un grupo hidroxilo), 2) un grupo alcoxilo de C_{1-6} (dicho grupo alcoxilo de C_{1-6} es sustituido con uno o más átomos halógenos iguales o diferentes), 3) un grupo carboxilo, 4) un grupo -COO-alquilo de C_{1-6}, y 5) un grupo ciano), o (4) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: 1) un átomo de halógeno, y 2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), (con la condición que R^3 y R^4 no sean simultáneamente átomos de hidrógeno), o una sal del mismo.

11. El compuesto de conformidad con la reivindicación 1, caracterizado además porque R^1 es 1) $-CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es (a) un átomo de hidrógeno, (b) un grupo arilo (dicho grupo arilo es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, c) un grupo carboxilo, d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y e) un grupo alcoxilo de C_{1-6}), (c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), (d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, c) un grupo arilo (dicho

grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)); d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv): (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo oxo, y (iv) un grupo alcoxilo de C_{1-6}), e) un grupo alcoxilo de C_{1-6}, y f) un grupo carboxilo), (e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, o (f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), (g) un grupo alcoxilo de C_{1-6}, o (h) un grupo heterocíclico monocíclico no saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o (i) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los

siguientes a) al i): a) un átomo de halógeno, b) un grupo hidroxilo, c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), d) un grupo carboxilo, e) un grupo -CO-alquilo de C_{1-6}, f) -CO-$NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, g) un grupo oxo, h) -$NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y i) un grupo alcoxilo de C_{1-6}) (con la condición que R^5 y R^6 no sean simultáneamente átomos de hidrógeno), 2) -$COOR^{10}$ en donde R^{10} es (a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al d): a) un grupo hidroxilo, b) -$NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, c) un grupo alcoxilo de C_{1-6}, y d) un grupo arilo), o (b) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), 3) -COR^{11} en donde R^{11} es (a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o

diferentes seleccionados de los siguientes a) al h): a) un átomo de halógeno, b) un grupo hidroxilo, c) $-NR^{28}R^{29}$ en donde R^{28} y R^{29} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, un grupo -CO-cicloalquilo, o un grupo $-S(=O)_2$-alquilo de C_{1-6}, o R^{28} y R^{29} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, d) $-CO-NR^{30}R^{31}$ en donde R^{30} y R^{31} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{30} y R^{31} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, e) un grupo alcoxilo de C_{1-6}, f) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo alcoxilo de C_{1-6}, y (iv) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), g) un grupo carboxilo, y h) un grupo ariloxilo), (b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) y b): a) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), o (c) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes

seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), (d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) a (3): (1) un átomo de halógeno, (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), y (3) un grupo alcoxilo de C_{1-6}), o (e) un grupo carboxilo, 4) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (d): (a) un grupo carboxilo, (b) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más, iguales o diferentes -CO-$NR^{32}R^{33}$ en donde R^{32} y R^{33} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6}), o R^{32} y R^{33} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno), (c) -CO-$NR^{34}R^{35}$ en donde R^{34} y R^{35} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{34} y R^{35} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y (d) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes))), 5) un grupo cicloalquilo, 6) -$S(=O)_2$-R^{12} en donde R^{12} es un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es sustituido con uno o más átomos halógenos iguales o diferentes), o un grupo arilo (dicho grupo

arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un átomo de halógeno, y b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), 7) -C(=NCN)-R^{13} en donde R^{13} es un grupo alquilo de C_{1-6}, 8) -C(=NCN)$NR^{14}R^{15}$ en donde R^{14} y R^{15} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{14} y R^{15} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, 9) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (f): (a) un grupo carboxilo, (b) un átomo de halógeno, (c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, y c) un grupo alcoxilo de C_{1-6}), (d) -$NR^{38}R^{39}$ en donde R^{38} y R^{39} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, un grupo -CO-alquilo de C_{1-6}, -CO-$NR^{40}R^{41}$ en donde R^{40} y R^{41} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo alcoxilo de C_{1-6}, o R^{40} y R^{41} opcionalmente forman junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o -$S(=O)_2$-R^{42} en donde R^{42} es un grupo alquilo de C_{1-6}), o R^{38} y R^{39} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más grupos oxo), (e) -CO-$NR^{43}R^{44}$ en donde R^{43} y R^{44} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{43} y R^{44} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico

monocíclico saturado que contiene nitrógeno, y (f) un grupo -COO-alquilo de C_{1-6}), o 10) un grupo heterocíclico monocíclico no saturado de 5 miembros ó de 6 miembros (dicho grupo heterocíclico es sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (a) a (h): (a) un grupo carboxilo, (b) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un átomo de halógeno, b) un grupo hidroxilo, y c) un grupo alcoxilo de C_{1-6}), (c) un grupo cicloalquilo, (d) un átomo de halógeno, (e) -CO-$NR^{45}R^{46}$ en donde R^{45} y R^{46} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{45} y R^{46} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno), (f) un grupo -COO-alquilo de C_{1-6}, (g) un grupo ciano, y (h) un grupo alcoxilo de C_{1-6}), o una sal del mismo.

12. El compuesto de conformidad con la reivindicación 1, o una sal del mismo, caracterizado además porque se selecciona de los siguientes: (1) 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-3-(piridin-3-il)pirrolidina; (2) clorhidrato de 1-[5-ciclopropil-1-(piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (3) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina; (4) 1-[1-(1-carbamoilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (5) 1-{1-[1-(2-carboxifenil-carbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (6) 1-{5-ciclopropil-1-[1-(2-hidroximetilfenil-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (7) 1-{5-ciclopropil-1-[1-(1-hidroximetilciclopropilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (8) 1-{5-ciclopropil-1-[1-(2-

hidroxietilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (9) 1-{5-ciclopropil-1-[1-(2-hidroxi-1,1-dimetiletilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (10) 1-{1-[1-(2-acetilaminoetilcarbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (11) clorhidrato de 1-{1-[1-(2-aminoetilcarbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (12) 1-{5-ciclopropil-1-[1-(1,1-dioxotiomorfolina-4-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (13) clorhidrato de 1-{5-ciclopropil-1-[1-(2-dimetilaminoetilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (14) 1-{5-ciclopropil-1-[1-(4-hidroxipiperidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (15) 1-{1-[1-(azetidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (16) 1-{5-ciclopropil-1-[1-(3-hidroxipirrolidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (17) 1-{5-ciclopropil-1-[1-(2-piperidin-1-il-etilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (18) 1-{5-ciclopropil-1-[1-(4,4-difluoropiperidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (19) 1-{5-ciclopropil-1-[1-(3,3-difluoropirrolidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (20) 1-{5-ciclopropil-1-[1-(3-hidroxiazetidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (21) 1-(5-ciclopropil-1-{1-[(R)-3-hidroxipirrolidin-1-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (22) 1-(5-ciclopropil-1-{1-[(S)-3-hidroxipirrolidin-1-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina;

(23) 1-(5-ciclopropil-1-{1-[(S)-2-hidroxi-1-metietilarbamoil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (24) 1-{5-ciclopropil-1-[1-(4-hidroximetilpiperidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (25) 1-{1-[1-(4-carboxipiperidin-1-carbonil)-piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (26) 1-{5-ciclopropil-1-[1-(3-oxopiperazin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (27) 1-(5-ciclopropil-1-{1-[(S)-2-hidroximetilpirrolidin-1-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (28) 1-{5-ciclopropil-1-[1-(3-hidroximetilazetidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (29) clorhidrato de 1-{5-ciclopropil-1-[1-(4-metilpiperazin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (30) clorhidrato de 1-{5-ciclopropil-1-[1-(4-isopropilpiperazin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (31) 1-{1-[1-(4-acetilpiperazin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (32) 1-(5-ciclopropil-1-{1-[(R)-3-hidroxipiperidin-1-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (33) 1-{1-[1-(4-carbamoilpiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (34) 1-{1-[1-(3-carbamoilazetidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (35) clorhidrato de 1-{1-[1-(4-aminopiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (36) clorhidrato de 1-{1-[1-(3-aminopirrolidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (37) clorhidrato de 1-{5-ciclopropil-1-[1-(piperidin-4-il-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina;

(38) clorhidrato de 1-{5-ciclopropil-1-[1-(4-dimetilaminopiperidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (39) 1-{1-[1-(4-acetilaminopiperidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (40) 1-{1-[1-(3-acetilaminopirrolidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (41) clorhidrato de 1-{5-ciclopropil-1-[1-(3-dimetilaminopirrolidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (42) clorhidrato de 1-{5-ciclopropil-1-[1-(1-metilpiperidin-4-il-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (43) 1-{1-[1-(1-acetilpiperidin-4-il-carbamoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (44) 1-{5-ciclopropil-1-[1-(4-oxopiperidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (45) 1-{1-[1-(3-acetilaminoazetidin-1-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (46) 1-{5-ciclopropil-1-[1-(3-oxopirrolidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (47) 1-{5-ciclopropil-1-[1-(2,2,2-trifluoroetilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (48) 1-{5-ciclopropil-1-[1-(3,3,4,4-tetrafluoro-pirrolidin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (49) 1-(5-ciclopropil-1-{1-[(S)-1-hidroximetil-2-metilpropilcarbamoil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (50) 1-(1-{1-[(S)-1-bencil-2-hidroxietilcarbamoil]-piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (51) 1-(5-ciclopropil-1-{1-[(S)-2-hidroxi-1-feniletilcarbamoil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (52) 1-(5-ciclopropil-1-{1-

[(S)-1-hidroximetil-3-metilbutilcarbamoil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (53) 1-{5-ciclopropil-1-[1-(2-hidroxifenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (54) 1-{5-ciclopropil-1-[1-(1-hidroximetilciclopentil-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (55) 1-[1-(1-bencensulfonilaminocarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (56) 1-[5-ciclopropil-1-(1-metansulfonilaminocarbonilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (57) 1-[5-ciclopropil-1-(1-metoxicarbonilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (58) 1-{5-ciclopropil-1-[1-(2-hidroxietoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (59) clorhidrato de 1-{5-ciclopropil-1-[1-(2-dimetilaminoetoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (60) clorhidrato de 1-{5-ciclopropil-1-[1-(2-piperidin-1-il-etoxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (61) clorhidrato de 1-{5-ciclopropil-1-[1-(piperidin-4-il-oxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (62) clorhidrato de 1-{5-ciclopropil-1-[1-(1-metilpiperidin-4-il-oxicarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (63) 1-{1-[1-(1-acetilpiperidin-4-il-oxicarbonil)-piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (64) 1-[1-(1-ciclopropancarbonilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (65) 1-{5-ciclopropil-1-[1-(2-hidroxiacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (66) 1-(5-ciclopropil-1-{1-[1-(4-fluorofenil)-ciclopropancarbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-

trifluorometilfenil)]pirrolidina; (67) clorhidrato de 1-{5-ciclopropil-1-[1-(2-dimetilaminoacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (68) 1-{1-[1-(2-acetilaminoacetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (69) 1-{5-ciclopropil-1-[1-(1-metilciclopropancarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (70) 1-{1-[1-(2-acetilamino-2-metilpropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (71) 1-(1-{1-[(S)-2-acetilaminopropionil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (72) 1-(1-{1-[(S)-2-acetilamino-3-metilbutiril]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (73) 1-{5-ciclopropil-1-[1-(3,3,3-trifluoropropionil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (74) 1-(5-ciclopropil-1-{1-[(S)-5-oxopirrolidin-2-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (75) 1-{1-[1-(3-acetilaminopropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (76) 1-{5-ciclopropil-1-[1-(3-hidroxi-2,2-dimetilpropionil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (77) clorhidrato de 1-{1-[1-(2-aminoacetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (78) 1-{5-ciclopropil-1-[1-(1-hidroximetil-ciclopropancarbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (79) clorhidrato de 1-{1-[1-(2-amino-2-metilpropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (80) 1-{5-ciclopropil-1-[1-(4-hidroxibutiril)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (81) clorhidrato de 1-(5-ciclopropil-1-{1-[(S)-pirrolidin-2-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (82) clorhidrato de 1-(5-ciclopropil-1-{1-[(S)-1-

metilpirrolidin-2-carbonil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (83) clorhidrato de 1-{1-[1-(3-aminopropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (84) clorhidrato de 1-(1-{1-[(S)-2-amino-3-metilbutiril]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (85) clorhidrato de 1-{5-ciclopropil-1-[1-(2-metilaminoacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (86) clorhidrato de 1-{5-ciclopropil-1-[1-(piperidin-4-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (87) 1-{5-ciclopropil-1-[1-(2-isobutirilaminoacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (88) 1-{1-[1-(2-ciclopropancarbonilaminoacetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (89) 1-(1-{1-[(S)-1-acetilpirrolidin-2-carbonil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (90) 1-{5-ciclopropil-1-[1-(2-metansulfonilaminoacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (91) 1-{1-[1-(1-acetilpiperidin-4-carbonil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (92) clorhidrato de 1-{5-ciclopropil-1-[1-(1-metilpiperidin-4-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (93) 1-{1-[1-(3-carbamoilpropionil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (94) clorhidrato de 1-[1-(1-carbamoilmetilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (95) clorhidrato de 1-[5-ciclopropil-1-(1-metilcarbamoilmetilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (96) clorhidrato de 1-{1-[1-(1-carbamoil-1-metiletil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-

trifluorometilfenil)]pirrolidina; (97) clorhidrato de 1-{1-[1-(2-carbamoiletil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (98) clorhidrato de 1-[5-ciclopropil-1-(1-ciclopropilmetilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (99) clorhidrato de 1-[5-ciclopropil-1-(1-ciclopropilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (100) clorhidrato de 1-[5-ciclopropil-1-(1-dimetilcarbamoilmetilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (101) clorhidrato de 1-[1-(1-carboximetilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (102) clorhidrato de 1-[1-(1-carboxietilpiperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (103) clorhidrato de 1-{1-[1-(1-carbamoiletil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (104) clorhidrato de 1-{1-[1-(2-carboxi-2-metilpropil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (105) clorhidrato de 1-{1-[1-(2-carbamoil-2-metilpropil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (106) clorhidrato de 1-{1-[1-(1-carbamoilciclopropilmetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (107) clorhidrato de 1-(5-ciclopropil-1-{1-[1-(2-hidroxietilcarbamoil)ciclopropilmetil]piperidin-4-il}-1H-pirazol-4-carbonil)-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (108) 1-[5-ciclopropil-1-(1-trifluorometansulfonilpiperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (109) 1-{5-ciclopropil-1-[1-(2,2,2-trifluoroetansulfonil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (110) 1-{1-[1-(1-cianoiminoetil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (111) 1-(1-{1-[cianoimino(metilamino)metil]piperidin-4-il}-5-ciclopropil-1H-pirazol-4-carbonil)-[(S)-3-

(2-trifluorometilfenil)]pirrolidina; (112) 1-{1-[1-(N-cianocarbamimidoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (113) ácido 4-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoico; (114) ácido 3-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoico; (115) ácido 5-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiofen-2-carboxílico; (116) ácido 2-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)tiazol-4-carboxílico; (117) clorhidrato de 1-{5-ciclopropil-1-[1-(5-metil-4H-[1,2,4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (118) clorhidrato de 1-{5-ciclopropil-1-[1-(5-ciclopropil-4H-[1,2,4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (119) clorhidrato de 1-{5-ciclopropil-1-[1-(5-hidroximetil-4H-[1,2,4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)] pirrolidina; (120) clorhidrato de 1-{5-ciclopropil-1-[1-(5-trifluorometil-4H-[1,2,4]triazol-3-il)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (121) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(R)-3-(2-trifluorometilfenil)]pirrolidina; (122) 1-{5-ciclopropil-1-[1-(1-metilciclopropil-carbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(R)-3-(2-trifluorometilfenil)]-pirrolidina; (123) 1-{5-ciclopropil-1-[1-(1-isopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(R)-3-(2-trifluorometilfenil)]pirrolidina; (124) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (125) 1-{5-ciclopropil-1-[1-(1-isopropilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (126) 1-{5-ciclopropil-1-[1-(1-metilciclopropilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (127) clorhidrato de (-)-3-(4-fluorofenil)-3-hidroximetil-

1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina; (128) clorhidrato de (+)-3-(4-fluorofenil)-3-hidroximetil-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina; (129) clorhidrato de 1-[5-ciclopropil-1-(1-pirazin-2-il-piperidin-4-il)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]-pirrolidina; (130) 1-[1-(trans-4-carbamoilciclohexil)-5-ciclopropil-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (131) 1-[5-ciclopropil-1-(trans-4-ureidociclohexil)-1H-pirazol-4-carbonil]-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (132) 1-{5-ciclopropil-1-[trans-4-(1H-tetrazol-5-il)ciclohexil]-1H-pirazol-4-carbonil}-[(S)-3-(2-trifluorometilfenil)]pirrolidina; (133) 1-{5-(1-metilciclopropil)-1-[1-(4-trifluorometilfenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina; (134) 1-{1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-5-(1-metoxiciclopropil)-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (135) 1-{1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-fenil-3-trifluorometil-pirrolidina; (136) 3-(2-clorofenil)-1-{5-ciclopropil-1-[1-(2,4-difluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina; (137) 3-(2-cloropiridin-3-il)-1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina; (138) 1-{1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-5-(2,2,3,3-tetrametilciclopropil)-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina; (139) 1-{5-ciclohexil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina; (140) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometoxifenil)pirrolidina; (141) 1-{5-ciclopropil-1-[1-(4-trifluorometilfenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (142) 1-(5-ciclopropil-1-{1-[(S)-1-carboxi-2-metilpropil)metilcarbamoil]piperidin-4-il}-1H-pirazol-4-carbonil)-3-(2-

trifluorometilfenil)pirrolidina; (143) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)-piperidin-4-il]-1H-pirazol-4-carbonil}-3-metoxi-3-(2-trifluorometilfenil)pirrolidina; (144) 1-{1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-5-(1-hidroximetilciclopropil)-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (145) 1-{5-ciclopropil-1-[1-(tiazol-2-ilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (146) 1-{1-[1-(isopropoxicarbamoil)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (147) 1-{5-ciclopropil-1-[1-(4-fluorobencilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (148) 1-{1-[1-(2,3-dihidroindol-1-carbonil)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina; (149) 1-{1-[1-(2,3-dihidro[1,4]oxazin-4-carbonil)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina; (150) 1-{5-ciclopropil-1-[1-(2,6-dicloropiridin-3-ilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (151) 1-{5-(1-metilciclopropil)-1-[1-(2,3,4,5-tetrahidrobenzo[b]azepin-1-carbonil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina; (152) 4-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)benzoato de etilo; (153) 1-[1-(1-benciloxicarbonil-piperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-3-(piridin-3-il)pirrolidina; (154) 1-{1-[1-(3-carboxi-3-metil-butiril)-piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)-pirrolidina; (155) 1-{5-ciclopropil-1-[1-(2-fenoxiacetil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina; (156) 1-{1-[1-(3-clorobenzoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina; (157) 1-{1-[1-(2-clorobenzoil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina; (158) 1-[5-ciclopropil-1-(1-oxalilpiperidin-4-il)-1H-pirazol-4-carbonil]-3-(2-trifluorometilfenil)pirrolidina; (159) 1-{1-[1-(4-clorobenzoil)-piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(piridin-3-il)-pirrolidina; (160) 1-(5-

ciclopropil-1-{1-[2-(4-fluorofenil)acetil]piperidin-4-il}-1H-pirazol-4-carbonil)-3-(piridin-3-il)pirrolidina; (161) 1-{5-ciclopropil-1-[1-(3-trifluorometilbenzoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)-pirrolidina; (162) 1-{5-ciclopropil-1-[1-(3-metoxibenzoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina; (163) clorhidrato de 1-{1-[1-(4-fluorobencil)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (164) 1-[1-(1-bencensulfonil-piperidin-4-il)-5-ciclopropil-1H-pirazol-4-carbonil]-3-(piridin-3-il)pirrolidina; (165) 1-{1-[1-(4-carbamoilfenil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (166) 1-{5-ciclopropil-1-[1-(4-hidroximetilfenil)-piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (167) 1-{1-[1-(5-carbamoil-piridin-2-il)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (168) 1-{1-[1-(4-aminofenil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (169) 1-(5-ciclopropil-1-{1-[4-(2-oxooxazolidin-3-il)fenil]piperidin-4-il}-1H-pirazol-4-carbonil)-3-(2-trifluorometilfenil)pirrolidina; (170) 1-(5-ciclopropil-1-{1-[4-(3-metoxiureido)fenil]piperidin-4-il}-1H-pirazol-4-carbonil)-3-(2-trifluorometilfenil)-pirrolidina; (171) 1-{5-ciclopropil-1-[1-(4-metansulfonilaminofenil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (172) 1-[1-(1-etoxicarbamoilpiperidin-4-il)-5-(1-metilciclopropil)-1H-pirazol-4-carbonil]-3-(2-trifluorometilfenil)pirrolidina; (173) 1-[1-(5-cloropiridin-2-il)azetidin-3-il]-5-ciclopropil-1H-pirazol-4-carbonil]-3-(2-trifluorometilfenil)pirrolidina; (174) 1-{1-[1-(5-cloro-piridin-2-il)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-metoximetil-3-fenilpirrolidina; (175) 1-{1-[1-(5-ciano-piridin-2-il)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (176) clorhidrato de 3-(2-acetoxietil)-3-(4-fluorofenil)-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-

carbonil}pirrolidina; (177) clorhidrato de {(3S*,4R*)-3-metil-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}-4-fenilpirrolidina; (178) 6-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)nicotinato de metilo; (179) 2-{1-[5-(1-metilciclopropil)-1-(1-pirimidin-2-il-piperidin-4-il)-1H-pirazol-4-carbonil]pirrolidin-3-il}benzoato de metilo; (180) clorhidrato de 3-(2-hidroximetilfenil)-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina; (181) 1-[5-ciclopropil-1-(1-piridin-2-il-piperidin-4-il)-1H-pirazol-4-carbonil]-3-hidroxi-3-(piridin-3-il)pirrolidina; (182) 1-{1-[1-(4-acetilaminofenil)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; (183) 4-(4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)-pirrolidin-1-carbonil]pirazol-1-il}piperidin-1-il)-3-fluorobenzoato de sodio; (184) 3-(2-cianofenil)-1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}pirrolidina; (185) clorhidrato de 3-hidroximetil-1-{1-[1-(4-metoxipirimidin-2-il)piperidin-4-il]-5-(1-metilciclopropil)-1H-pirazol-4-carbonil}-3-fenilpirrolidina; (186) clorhidrato de 3-(3,5-difluorofenil)-3-hidroximetil-1-{5-(1-metilciclopropil)-1-[1-(pirimidin-2-il)piperidin-4-il]-1H-pirazol-4-carbonil}-pirrolidina; (187) 1-{1-[1-(3-cloro-piridin-2-il)piperidin-4-il]-5-ciclopropil-1H-pirazol-4-carbonil}-3-(piridin-3-il)pirrolidina; (188) 1-{5-ciclopropil-1-[1-(2-fluorofenilcarbamoil)piperidin-4-il]-1H-pirazol-4-carbonil}-3-(tiazol-2-il)pirrolidina; (189) ácido (S)-2-[(trans-4-{5-ciclopropil-4-[3-(2-trifluorometilfenil)-pirrolidin-1-carbonil]-pirazol-1-il}-ciclohexancarbonil)-metil-amino]-3-metilbutírico; (190) 1-{5-(1-metilciclopropil)-1-[trans-4-(2-fluorofenilcarbamoil)-ciclohexil]-1H-pirazol-4-carbonil}-3-(2-trifluorometilfenil)pirrolidina; y (191) ácido cis-4-{5-(1-metilciclopropil)-4-[3-(2-trifluorometilfenil)-pirrolidin-1-carbonil]-pirazol-1-il)-ciclohexancarboxílico.

13. Una composición farmacéutica que comprende un compuesto como el que se reclama en cualquiera de las reivindicaciones 1 a 12, o una sal del

mismo.

14. Un inhibidor de 11βHSD1 que comprende un compuesto como el que se reclama en cualquiera de las reivindicaciones 1 a 12, o una sal del mismo.

15. Un agente para el tratamiento o profilaxis de una patología que involucra glucocorticoide, que comprende un compuesto como el que se reclama en cualquiera de las reivindicaciones 1 a 12, o una sal del mismo.

16. El agente de conformidad con la reivindicación 15, caracterizado además porque la patología que involucra glucocorticoide es (1) una enfermedad metabólica que incluye diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión o hígado graso, (2) un síndrome metabólico, (3) un evento vascular fatal que incluye infarto cardíaco o apoplejía cerebral, (4) hiperorexia, (5) una enfermedad neurodisfuncional que incluye disgnosia, enfermedad neurodegenerativa, desórdenes emocionales, esquizofrenia o estímulo del apetito, (6) una enfermedad asociada con la función de inmunidad disminuida, (7) glaucoma, u (8) osteoporosis.

17. Un método para inhibir 11βHSD1, que comprende administrar una cantidad farmacéuticamente eficaz de un compuesto como el que se reclama en cualquiera de las reivindicaciones 1 a 12, o una sal del mismo.

18. Un método para tratar o prevenir una patología que involucra glucocorticoide, que comprende administrar una cantidad farmacéuticamente eficaz de un compuesto como el que se reclama en cualquiera de las reivindicaciones 1 a 12, o una sal del mismo.

19. El método que se reclama en la reivindicación 18, en donde la patología que involucra glucocorticoide es (1) una enfermedad metabólica que incluye diabetes, resistencia a insulina, complicaciones diabéticas, obesidad,

hiperlipidemia, hipertensión o hígado graso, (2) un síndrome metabólico, (3) un evento vascular fatal que incluye infarto cardíaco o la apoplejía cerebral, (4) hiperorexia, (5) una enfermedad neurodisfuncional que incluye disgnosia, el enfermedad neurodegenerativa, desórdenes emocionales, esquizofrenia o estímulo del apetito, (6) una enfermedad asociada con la función de inmunidad disminuida, (7) glaucoma, u (8) osteoporosis.

20. El uso de un compuesto como el que se reclama en cualquiera de las reivindicaciones 1 a 12, o una sal del mismo, para la producción de un inhibidor de 11βHSD1.

21. El uso de un compuesto como el que se reclama en las reivindicaciones 1 a 12, o una sal del mismo, para la producción de un agente para el tratamiento o profilaxis de una patología que involucra glucocorticoide.

22. El uso que se reclama en la reivindicación 21, en donde la patología que involucra glucocorticoide es (1) una enfermedad metabólica que incluye diabetes, resistencia a insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión o hígado graso, (2) un síndrome metabólico, (3) un evento vascular fatal que incluye infarto cardíaco o apoplejía cerebral, (4) hiperorexia, (5) una enfermedad neurodisfuncional que incluye disgnosia, enfermedad neurodegenerativa, desórdenes emocionales, esquizofrenia o estímulo del apetito, (6) una enfermedad asociada con la función de inmunidad disminuida, (7) glaucoma, u (8) osteoporosis.

23. Un paquete comercial que comprende un material escrito que declara que la composición farmacéutica que se reclama en la reivindicación 13 puede o debe ser usada para el tratamiento o profilaxis de una enfermedad seleccionada de (1) una enfermedad metabólica que incluye diabetes, resistencia a

insulina, complicaciones diabéticas, obesidad, hiperlipidemia, hipertensión o hígado graso, (2) un síndrome metabólico, (3) un evento vascular fatal que incluye infarto cardíaco o apoplejía cerebral, (4) hiperorexia, (5) una enfermedad neurodisfuncional que incluye disgnosia, enfermedad neurodegenerativa, desórdenes emocionales, esquizofrenia o estímulo del apetito, (6) una enfermedad asociada con la función de inmunidad disminuida, (7) glaucoma, u (8) osteoporosis.

24. La composición farmacéutica de conformidad con la reivindicación 13, caracterizada además porque es utilizada en combinación con 1 a 3 agentes seleccionados de los siguientes (1) a (5): (1) un agente para el tratamiento o profilaxis de hiperlipidemia, (2) un agente para el tratamiento o profilaxis de obesidad, (3) un agente para el tratamiento o profilaxis de diabetes, (4) un agente para el tratamiento o profilaxis de complicaciones diabéticas, (5) un agente para el tratamiento o profilaxis de hipertensión.

25. El inhibidor de 11βHSD1 de conformidad con la reivindicación 14, caracterizado además porque es usado en combinación con 1 a 3 agentes seleccionados de los siguientes (1) a (5): (1) un agente para el tratamiento o profilaxis de hiperlipidemia, (2) un agente para el tratamiento o profilaxis de obesidad, (3) un agente para el tratamiento o profilaxis de diabetes, (4) un agente para el tratamiento o profilaxis de complicaciones diabéticas, (5) un agente para el tratamiento o profilaxis de hipertensión.

26. El agente de conformidad con la reivindicación 15 o 16, caracterizado además porque va a ser utilizado en combinación con 1 a 3 agentes seleccionados de los siguientes (1) a (5): (1) un agente para el tratamiento o profilaxis de hiperlipidemia, (2) un agente para el tratamiento o profilaxis de obesidad, (3) un agente para el tratamiento o profilaxis de diabetes, (4) un agente para el tratamiento

o profilaxis de complicaciones diabéticas, (5) un agente para el tratamiento o profilaxis de hipertensión.

27. El método que se reclama en la reivindicación 17, que además comprende administrar de 1 a 3 agentes seleccionados de los siguientes (1) a (5): (1) un agente para el tratamiento o profilaxis de hiperlipidemia, (2) un agente para el tratamiento o profilaxis de obesidad, (3) un agente para el tratamiento o profilaxis de diabetes, (4) un agente para el tratamiento o profilaxis de complicaciones diabéticas, (5) un agente para el tratamiento o profilaxis de hipertensión.

28. Un agente farmacéutico que comprende de 1 a 3 agentes seleccionados de los siguientes (1) a (5) y un compuesto como el que se reclama en cualquiera de las reivindicaciones 1 a 12 o una sal del mismo, en combinación: (1) un agente para el tratamiento o profilaxis de hiperlipidemia, (2) un agente para el tratamiento o profilaxis de obesidad, (3) un agente para el tratamiento o profilaxis de diabetes, (4) un agente para el tratamiento o profilaxis de complicaciones diabéticas, (5) un agente para el tratamiento o profilaxis de hipertensión.

29. El método para tratar o prevenir una patología que involucra glucocorticoide que se reclama en la reivindicación 18 ó 19, que además comprende administrar de 1 a 3 agentes seleccionados de los siguientes (1) a (5): (1) un agente para el tratamiento o profilaxis de hiperlipidemia, (2) un agente para el tratamiento o profilaxis de obesidad, (3) un agente para el tratamiento o profilaxis de diabetes, (4) un agente para el tratamiento o profilaxis de complicaciones diabéticas, (5) un agente para el tratamiento o profilaxis de hipertensión.

30. El uso que se reclama en la reivindicación 20, en donde será combinado con el uso de 1 a 3 agentes seleccionados de los siguientes (1) a (5): (1) un agente para el tratamiento o profilaxis de hiperlipidemia, (2) un agente para el

tratamiento o profilaxis de obesidad, (3) un agente para el tratamiento o profilaxis de diabetes, (4) un agente para el tratamiento o profilaxis de complicaciones diabéticas, (5) un agente para el tratamiento o profilaxis de hipertensión.

31. El uso que se reclama en la reivindicación 21 o 22, en donde será combinado con el uso de 1 a 3 agentes seleccionados de los siguientes (1) a (5): (1) un agente para el tratamiento o profilaxis de hiperlipidemia, (2) un agente para el tratamiento o profilaxis de obesidad, (3) un agente para el tratamiento o profilaxis de diabetes, (4) un agente para el tratamiento o profilaxis de complicaciones diabéticas, (5) un agente para el tratamiento o profilaxis de hipertensión.

32. La composición farmacéutica de conformidad con la reivindicación 13, caracterizada además porque es usada para suprimir el incremento del nivel de glucocorticoide en la sangre, utilizada en combinación con un agente farmacéutico que eleva el nivel de glucocorticoide en la sangre.

33. El inhibidor de 11βHSD1 de conformidad con la reivindicación 14, caracterizado además porque es utilizado para suprimir el incremento del nivel de glucocorticoide en la sangre, utilizado en combinación con un agente farmacéutico que eleva el nivel de glucocorticoide en la sangre.

34. El método que se reclama en la reivindicación 17, que además comprende administrar un agente farmacéutico que eleva el nivel de glucocorticoide en la sangre.

35. El uso que se reclama en la reivindicación 21, en donde es para suprimir el incremento del nivel de glucocorticoide en la sangre utilizado en combinación con un agente farmacéutico que eleva el nivel de glucocorticoide en la sangre.

36. Un método para suprimir el incremento del nivel de

glucocorticoide en la sangre, que comprende administrar un agente farmacéutico que eleva el nivel de glucocorticoide en la sangre y el inhibidor de 11βHSD1 que se reclama en la reivindicación 14.

37. 2-[(S)-2-Nitro-1-(2-trifluorometilfenil)etil]malonato de dimetilo.

38. (S)-2-Oxo-4-(2-trifluorometilfenil)pirrolidin-3-carboxilato de metilo.

39. (S)-4-(2-Trifluorometilfenil)pirrolidin-2-ona.

40. (S)-3-(2-Trifluorometilfenil)pirrolidina o una sal de la misma.

41. Un método para producir 2-[(S)-2-nitro-1-(2-trifluorometilfenil)etil]malonato de dimetilo, que comprende una etapa para hacer reaccionar 1-((E)-2-nitrovinil)-2-trifluorometilbenceno con malonato de dimetilo en presencia de 1-(3,5-bis-trifluorometilfenil)-3-((1S,2S)-2-dimetilaminociclohexil)-tiourea.

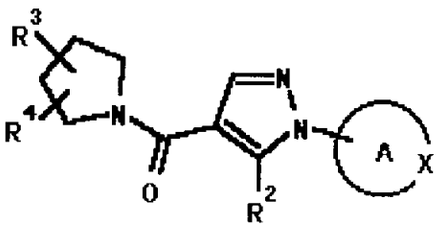
42. Un método para producir (S)-2-oxo-4-(2-trifluorometilfenil)pirrolidin-3-carboxilato de metilo, que comprende una etapa para reducción y cierre del anillo de 2-[(S)-2-nitro-1-(2-trifluorometilfenil)etil]malonato de dimetilo.

43. Un método para producir (S)-4-(2-trifluorometilfenil)pirrolidin-2-ona, que comprende una etapa para hidrólisis y descarbonación de (S)-2-oxo-4-(2-trifluorometilfenil)pirrolidin-3-carboxilato de metilo.

44. Un método para producir una sal de (S)-3-(2-trifluorometilfenil)pirrolidina, que comprende una etapa para reducción de (S)-4-(2-trifluorometilfenil)pirrolidin-2-ona y una etapa para tratar el compuesto resultante con un ácido para formar una sal.

RESUMEN DE LA INVENCION

La presente invención provee un compuesto representado por la fórmula siguiente [1'] o una sal del mismo:



[1']

en donde el anillo A, R^2, R^3, R^4 y X son iguales a los definidos en la descripción, y un agente para el tratamiento o profilaxis de una patología que involucra glucocorticoide, o un inhibidor de 11βHSD1, que contiene el compuesto o una sal del mismo.

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SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ____ PCT __X__ MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) Nº de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional :

(71)Solicitante(s) **JAPAN TOBACCO INC.**

(72) Inventor(es) **HIROSHI YAMAMOTO, YASUHIRO OHE, HIROYUKI GOTO, KAZUHITO HARADA, SHINJI YATA, JUN NISHIU, MAKOTO KAKUTANI, SHUNSUKE FUJII, KOTA ASAHINA, TAKASHI ITO**

(74) Apoderado: **DRA. MARGARITA CASTELLANOS ABONDANO**

(30) Prioridad	(31) No. Prioridad	32) Fecha	(33) País
	2005-168901	08/06/2005	JP
	60/692.039	17/06/2005	US
	2006-027097	03/02/2006	JP
	60/772.734	13/02/2006	US
	2006-138252	17/05/2006	JP

(85) Fecha inicio fase nacional:

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: **08/06/2006**
No. de solicitud **PCT/JP2006/311975**

(87) Publicación internacional
Fecha: **14/12/2006**
Nº publicación: **WO 2006/132436 A1**

(54) Titulo: **COMPUESTO HETEROCICLICO**

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) Nº de solicitud: 08-1136

22) Fecha de solicitud: 08-01-2008

(51) int. Cl.: C07D 401/14 ; A61K-401/14 A61P 9/12

(71)Solicitante(s) JAPAN TOBACCO INC.

(30) Prioridad	(31) Nº Prioridad	32) Fecha	(33) País
	2005-168901	08/06/2005	JP
	60/692.039	17/06/2005	US
	2006-027097	03/02/2006	JP
	60/772.734	13/02/2006	US
	2006-138252	17/05/2006	JP

(72) Inventor(es) HIROSHI YAMAMOTO Y OTROS

(74) Apoderado: MARGARITA CASTELLANOS ABONDANO

(85) Fecha límite inicio fase nacional:

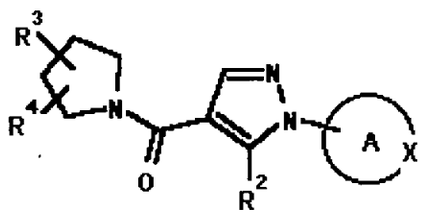
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 08/06/2006
Nº de solicitud PCT/JP2006/311975

(87) Publicación internacional
Fecha: 14/12/2006
Nº publicación: WO/2006/132436 A1

(54) Titulo: COMPUESTO HETEROCICLICO

Reivindicación(es):

1. Un compuesto representado por la fórmula siguiente [1']:



[1']

en donde: el anillo A es (1) un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o (2) un grupo cicloalquilo, dicho anillo A es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes R^1, dicho sustituyente R^1 es 1) un átomo de hidrógeno, 2) $-CONR^5R^6$ en donde R^5 y R^6 son iguales o diferentes y cada uno es (a) un átomo de hidrógeno, (b) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, c) un grupo carboxilo, d) un grupo de alquilo C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), y e) un grupo alcoxilo de C_{1-6}), (c) un grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido con uno o más grupos alquilo de C_{1-6} iguales o diferentes (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un grupo hidroxilo, y (ii) un grupo alcoxilo de C_{1-6})), (d) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: a) un grupo hidroxilo, b) un átomo de halógeno, c) un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (1) y (2): (1) un átomo de halógeno, y (2) grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), d) $-NR^{20}R^{21}$ en donde R^{20} y R^{21} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{20} y R^{21} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de lo siguiente (i) a (iv): (i) un átomo de halógeno, (ii) un grupo hidroxilo, (iii) un grupo oxo, y (iv) un grupo alcoxilo de C_{1-6}), e) un grupo alcoxilo de C_{1-6}, y f) un grupo carboxilo), (e) $-S(=O)_2-R^9$ en donde R^9 es un grupo arilo (dicho grupo arilo es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes (1) y (2): (1) un átomo de halógeno, y (2) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes)), o un grupo alquilo de C_{1-6}, (f) un grupo heterocíclico monocíclico saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al c): a) un grupo alquilo de C_{1-6}, b) un grupo -CO-alquilo de C_{1-6}, y c) un grupo oxo), (g) un grupo alcoxilo de C_{1-6}, o (h) un grupo heterocíclico monocíclico no saturado que contiene nitrógeno (dicho grupo heterocíclico es opcionalmente sustituido con uno o más átomos halógenos iguales o diferentes), o (i) R^5 y R^6 opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, o un grupo heterocíclico que es un anillo fusionado de dicho heterociclo y un anillo de carbono (ambos grupos heterocíclicos indicados son opcionalmente sustituidos con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al i): a) un átomo de halógeno, b) un grupo hidroxilo, c) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados del grupo siguiente: (i) un átomo de halógeno, (ii) un grupo hidroxilo, y (iii) un grupo alcoxilo de C_{1-6}), d) un grupo carboxilo, e) un grupo -CO-alquilo de C_{1-6}, f) $-CO-NR^{22}R^{23}$ en donde R^{22} y R^{23} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{22} y R^{23} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, g) un grupo oxo, h) $-NR^{24}R^{25}$ en donde R^{24} y R^{25} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo alquilo de C_{1-6}, o un grupo -CO-alquilo de C_{1-6}, o R^{24} y R^{25} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico monocíclico saturado que contiene nitrógeno, y i) un grupo alcoxilo de C_{1-6}), 3) $-COOR^{10}$ en donde R^{10} es (a) un grupo alquilo de C_{1-6} (dicho grupo alquilo de C_{1-6} es opcionalmente sustituido con uno o más sustituyentes iguales o diferentes seleccionados de los siguientes a) al d): a) un grupo hidroxilo, b) $-NR^{26}R^{27}$ en donde R^{26} y R^{27} son iguales o diferentes y cada uno es un átomo de hidrógeno, o un grupo alquilo de C_{1-6}, o R^{26} y R^{27} opcionalmente forman, junto con el átomo de nitrógeno al cual están unidos, un grupo heterocíclico ...

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No. 08-001136- -00000-0000
Fecha: 2008-01-08 16:23:50 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 718

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRÁMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION (X) MODELO DE UTILIDAD ( )	(X)	( )
- Indicación de que se solicita la concesión de una patente	(X)	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud	(X)	( )
- Descripción de la invención	(X)	( )
- Dibujos de ser estos pertinentes	( )	( )
- Comprobante de pago de las tasas establecidas	(X)	( )

COMPLETA (X) INCOMPLETA ( )

DISEÑO INDUSTRIAL ( )

- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud	( )	( )
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño	( )	( )
- Comprobante de pago de las tasas establecidas	( )	( )

COMPLETA ( ) INCOMPLETA ( )

EZQUEMA DE TRAZADO ( )

- 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 del Esquema de Trazado	( )	( )
- Comprobante de pago de las tasas establecidas	( )	( )

COMPLETA ( ) INCOMPLETA ( )

Firma responsable: FDO B

Fecha: 8 - ENE - 8

720

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CASTELLANOS ABONDANO MARGARITA
Apoderado(a) y/o Representante de
JAPAN TOBACCO INC.

REFERENCIA	Radicación No.	8 1136
	Solicitud internacional	PCT/JP2006/311975
	Fecha inicio fase nacional	08/01/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	1506

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 08 FEB. 2008.
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