Industria y Comercio
SUPERINTENDENCIA

PETITORIO

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

25/09/2007

SOLICITUD DE:

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

2. SOLICITANTE (71)

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

Dirección: 1-1, Doshomachi, 4-chome, Chuo-ku, Osaka-shi, Osaka 5410045, Japón

Domicilio: Osaka 5410045, Japón

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

3. REPRESENTANTE O APODERADO

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

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

4. INVENTOR (ES) (72)

1. **Hironobu MAEZAKI**
   c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED,
   17-85,
   Jusohonmachi, 2-chome,
   Yodogawa-ku,
   Osaka-shi,
   Osaka 5328686
   Japón
2. **Nobuhiro SUZUKI**
   c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED
   10 Wadai,
   Tsukuba-shi,
   Ibaraki 3004293,
   Japón

5. PCT (86)
Solicitud Internacional No. PCT/JP2006/304177 Fecha: 24 de febrero de 2006
Publicación Internacional No. WO2006/090915 A1 Fecha: 31 de agosto de 2006

6. Título (54)
COMPUESTOS DE PIRIDIL ACIDO ACETICO

7. Clasificación Internacional (51) C07D 213/055 A 61 K 31/4427
A 61 P 3/08

8. Prioridad SI☒ NO☐

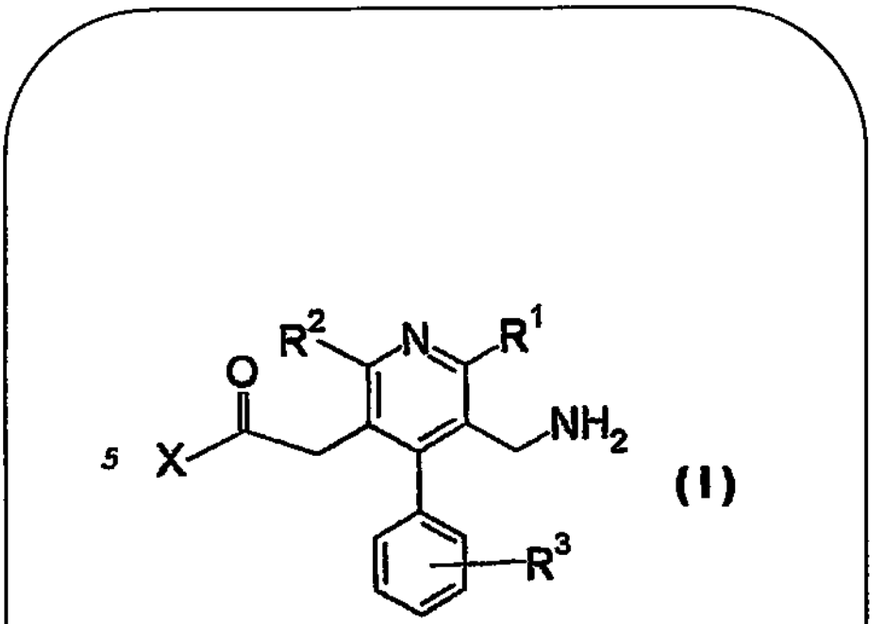
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
JP	25 de febrero de 2005	2005-052018

9. Comprobante de pago No.: 07-72,884 **Fecha:** 10 de septiembre de 2007

10 Anexos:

- [x] Comprobante de pago de la tasa de presentación de la solicitud por $ 482.000.oo.
- [ ] Comprobante de pago por reivindicación de prioridad.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [x] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros: VER HOJA DE DOCUMENTOS ANEXOS

11 FIGURA CARACTERÍSTICA



(I)

12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

AHP

44

ee

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a Nº 72-35
BOGOTA, D - COLOMBIA

179

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

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

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

14656
08085

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

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª Nº 72_35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

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

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª Nº 72_35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case; and the mere act of so stating exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

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

COPIA NOTARIO SEXTO (6) DEL CIRCULO
FOTOCOPIA CONCUERDA CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
10 SET 2007
ALEJANDRO VELEZ TARAJAS
NOTARIO

58

[redacted] todos los asuntos arriba determinados, pueden [redacted], transigir, conciliar, admitir los hechos del [redacted], recibir, renunciar, y ratificar los actos de [redacted]

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

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

en/in Osaka, Japan

por/by

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

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
30 SET 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

66

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: **JAPAN**

   This public document

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

Certified

5. at Osaka
6. DEC. 17. 2004
7. by the Ministry of Foreign Affairs
8. No. 04149
9. Seal/stamp:
10. Signature:

Tsutomu HIGUCHI

For the Minister for Foreign Affairs

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

18 SET 2007

PAB MENDEZ MARAJAS
NOTARIO (E)

大阪法務局所属　公証人役場

認証登簿　平成１６年 第　334　号

嘱託人 武田薬品工業株式会社 常務取締役　知的財産部長 秋元浩

は、本職の面前でこの証書に署名した。

よって、その署名が本人の自筆であることを証する。

平成　16　年　12　月　14　日

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

10 SET 2007

PABLO MENDEZ BARAJAS
NOTARIO (E)

大阪市西区江戸堀１丁目１０番８号（帝人殖産ビル内）

公証人　藤田清臣　役場において

大阪法務局所属

公証人　藤田清臣

8 8

REGISTER NUMBER 334 / 2004

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

Dated this 14th day of December, 2004

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

Kiyomi Fujita

Kiyomi Fujita
Notary attached
to The Osaka Legal
Affairs Bureau

9 A

THE OSAKA CHAMBER OF COMMERCE & INDUSTRY

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

November 17, 2004

To whom it may concern:

CERTIFICATE OF MEMBERSHIP

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

Company name: Takeda Pharmaceutical Company Limited

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

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

Membership Number: KT-01-00080

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
10 SET 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

The Osaka Chamber of Commerce & Industry

Yoshinobu Kobayashi
Authorized Signatory

A 2009149

THE OSAKA CHAMBER OF COMMERCE & INDUSTRY

NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

19 OCT 2007

PABLO BENDES BARAJAS
NOTARIO (E)

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2005 FEB -4 A 9:33

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

DIRECCION DE RELACIONES EXTERIORES

085744

LA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

EMBAJADA DE COLOMBIA - SECCION CONSULAR

Tokio, Japón, DICIEMBRE 20, 2004
No. 299

El encargado de las funciones consulares de Colombia
CERTIFICA:

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

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

Firma del Encargado de Funciones Consulares

Derechos: US$23.oo

RAFAEL RICARDO OROZCO
Segundo Secretario

10

総第 3603 号

証　　明

大阪法務局所属公証人　**藤田清臣**

平成 16年12 月14 日付

平成16年 登簿 第 334 号

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

平成16年12月17日
平成　　年　　月　　日

大阪法務局長　**梅津和宏**

NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME FUE PRESENTADO A LA VISTA
10 SET 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

CERTIFICATE

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

Date 04.12.17

Director of the Osaka Legal Affairs Bureau

11 #

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

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

Firma Ilegible

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

REGISTRO NÚMERO 334 / 2004

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

CONSULADO SEXTO (E) DEL CIRCULO DE SOCORRO HACE CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE SE TUVO A LA VISTA
14 SET 2007
PABLO [illegible] BARAJAS
NOTARIO (E)

Expedido hoy 14 de diciembre de 2004

10-8, Edobori 1-chome

Nishi-ku, Osaka, Japón

12 X

Firma ilegible

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

DOCUMENTO ANTERIOR EN JAPONÉS

(Anexo)

Texto en Japonés

CERTIFICADO

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

Fecha: 04.12.17

Director de la Oficina de Asuntos Legales de Tokio

APOSTILLA

(Convention de La Haye du 5 octubre

COMO NOTARIO EJECTO (2) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE SE TUVO A LA VISTA
10 SET 2007
PABLO [illegible] BARAJAS

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

La Cámara de Comercio e Industria de Osaka

Firma Ilegible

Yoshinobu Kobayashi

Signatario Autorizado

(Respaldo)

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

Firmado por RAFAEL RICARDO OROZCO, Segundo Secretario.

Pagados los derechos consulares.

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

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

11 SET 2007

PABLO MENDEZ BARAJAS
NOTARIO (E)

Es traducción fiel y completa de la cual se deja co[illegible] oficina para su confrontación.

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

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

MINISTERIO DE
RELACIONES EXTERIORES

313395

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 FEB -8 P 2:40

JEFE DE LEGALIZACIONES
BOGOTA D.C.

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

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

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

10 SET 2007

PABLO MENDEZ BARAJAS
NOTARIO (E)

1449

Certificado

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

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

8. **No. 04149**

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

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

MINISTERIO DE RELACIONES EXTERIORES · JAPÓN ·

Firma Ilegible

Tsutomu HIGUCHI

Por el Ministro de Relaciones Exteriores

LA CÁMARA DE COMERCIO E INDUSTRIA DE OSAKA

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

Noviembre 17 de 2004

A quién pueda interesar:

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
10 SET 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

CERTIFICADO DE MEMBRESÍA

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

Nombre de la compañía: Takeda Pharmaceutical Company Limited

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

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

Número de Membresía: KT-01-00080

MINISTERIO DE
RELACIONES EXTERIORES

313391

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

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 FEB -8 P 2:39

UCS
JEFE DE LEGALIZACIONES
BOGOTA D.C.

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE
BOGOTA, HAGO CONSTAR QUE ESA(S) FIRMA(S) DE
CONCEDE(N) CON LA FIRMA REGISTRADA POR
EL (ELLOS) EN ESTA NOTARIA
SANTAFE DE BOGOTA,
08 FEB 2005

CONSTA DE UNA HOJA(S) UTIL(ES)
DE EXTRACTO. EXPEDIDO CON COPIAS QUE LA
FOTOCOPIA CORRESPONDE CON EL ORIGINAL
QUE SE HA TENIDO A LA VISTA

10 SET 2007

PABLO ANDRES BARAJAS
NOTARIO (E)

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

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
31 August 2006 (31.08.2006)

(10) International Publication Number
WO 2006/090915 A1

(51) International Patent Classification:
C07D 213/55 (2006.01) *C07D 417/12* (2006.01)
C07D 213/56 (2006.01) *C07D 401/14* (2006.01)
C07D 401/12 (2006.01) *A61P 3/08* (2006.01)
C07D 413/12 (2006.01) *A61K 31/44* (2006.01)
C07D 405/12 (2006.01) *A61K 31/4427* (2006.01)
C07D 409/12 (2006.01)

(21) International Application Number:
PCT/JP2006/304177

(22) International Filing Date:
24 February 2006 (24.02.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2005-052018 25 February 2005 (25.02.2005) JP

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

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): MAEZAKI, Hironobu [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka, 5328686 (JP). SUZUKI, Nobuhiro [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 10, Wadai, Tsukuba-shi, Ibaraki, 3004293 (JP).

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

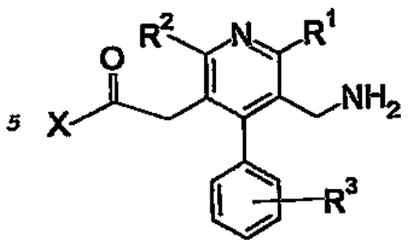
(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, 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) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, 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).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PYRIDYL ACETIC ACID COMPOUNDS



(I)

(57) Abstract: The present invention provides a compound represented by the formula (I): wherein R_1 is a C71-6#191 alkyl group optionally substituted by a C73-10#191 cycloalkyl group, R_2 is a C72-6#191 alkyl group, R_3 is a hydrogen atom, a C71-6#191 alkyl group or a halogen atom, and X is $-OR_6$ or $-NR_4R_5$ wherein R_4 and R_6 are each independently a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, R_5 is an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group or an optionally substituted hydroxy group, or R_4 and R_5 optionally form, together with the adjacent nitrogen atom, an optionally substituted nitrogen-containing heterocycle, or a salt thereof. The compound of the present invention has a superior peptidase inhibitory action and is useful as an agent for the prophylaxis or treatment of diabetes and the like.

WO 2006/090915 A1

DESCRIPTION

PYRIDYL ACETIC ACID COMPOUNDS

Technical Field

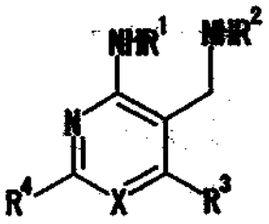
The present invention relates to a pyridyl acetic acid compound having a peptidase inhibitory activity, which is useful as an agent for the prophylaxis or treatment of diabetes and the like.

Background Art

Peptidase is known to relate to various diseases. Dipeptidyl dipeptidase-IV (hereinafter sometimes to be abbreviated as DPP-IV), which is one kind of peptidases, is serine protease that specifically binds with a peptide containing proline (or alanine) at the 2nd from the N-terminal and cleaves the C-terminal side of the proline (or alanine) to produce dipeptide. DPP-IV has been shown to be the same molecule as CD26, and reported to be also involved in the immune system. While the role of DPP-IV in mammals has not been entirely clarified, it is considered to play an important role in the metabolism of neuropeptides, activation of T cells, adhesion of cancer cells to endothelial cells, invasion of HIV into cells and the like. Particularly, from the aspect of glycometabolism, DPP-IV is involved in the inactivation of GLP-1 (glucagon-like peptide-1) and GIP (Gastric inhibitory peptide/Glucose-dependent insulinotropic peptide), which are incretins. With regard to GLP-1, moreover, it is known that the physiological activity of GLP-1 is markedly impaired because it has a short plasma half-life of 1-2 minutes, and GLP-1(9-36)amide, which is a degradation product by DPP-IV, acts on GLP-1 receptor as an antagonist, thus decomposing GLP-1 by DPP-IV. It is also known that suppression of degradation of GLP-1 by inhibiting DPP-IV activity leads to potentiation of physiological activity that GLP-1 shows, such as glucose concentration-dependent insulin secretagogue effect and the like. From these facts, a compound having a DPP-IV inhibitory activity

is expected to show effect on impaired glucose tolerance, postprandial hyperglycemia and fasting hyperglycemia observed in type I and type II diabetes and the like, obesity or diabetic complications associated therewith and the like.

As a compound having a DPP-IV inhibitory action, for example, a compound represented by the formula



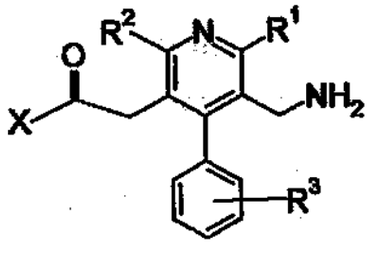
wherein X is N or CR^5 (wherein R^5 is hydrogen or lower alkyl); R^1 and R^2 are independently hydrogen or lower alkyl; R^3 is heterocyclic group or aryl, each optionally substituted by lower alkyl and the like; R^4 is lower alkyl and the like, or a salt thereof, has been reported (see WO03/068757).

However, there is no report on the compound of the present invention.

Disclosure of the Invention

There is a demand for the development of a compound having a peptidase inhibitory action, which is useful as an agent for the prophylaxis or treatment of diabetes and the like and superior in efficacy, duration of action, specificity, lower toxicity and the like.

The present inventors have first found that a compound represented by the formula (I):



(I)

wherein

R^1 is a C_{1-6} alkyl group optionally substituted by a C_{3-10} cycloalkyl group,

R^2 is a C_{2-6} alkyl group,

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

X is $-OR^6$ or $-NR^4R^5$

wherein R^4 and R^6 are each independently a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, R^5 is an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group or an optionally substituted hydroxy group, or R^4 and R^5 optionally form, together with the adjacent nitrogen atom, an optionally substituted nitrogen-containing heterocycle,

or a salt thereof

[hereinafter sometimes to be abbreviated as compound (I)], which is characterized by a chemical structure wherein an amino group is bonded to the 3-position via a methylene group; an optionally substituted phenyl group is bonded to the 4-position; an acyl group is bonded to the 5-position via a methylene group; and a C_{2-6} alkyl group is bonded to the 6-position, of the pyridine ring, has a superior peptidase inhibitory action and is useful as an agent for the prophylaxis or treatment of diabetes and the like. Based on this finding, the present inventors have conducted intensive studies and completed the present invention.

Accordingly, the present invention relates to

1) compound (I);

2) compound (I), wherein X is -OH;

3) compound (I), wherein R^1 is a C_{3-6} alkyl group;

4) compound (I), wherein R^3 is a C_{1-6} alkyl group;

5) compound (I), which is

[5-(aminomethyl)-2-ethyl-6-isobutyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid;

[5-(aminomethyl)-2,6-diisobutyl-4-(4-methylphenyl)pyridin-3-yl]acetic acid;

[5-(aminomethyl)-2-ethyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetic acid; or

1-{[5-(aminomethyl)-2-ethyl-4-(4-methylphenyl)-6-neopentylpyridin-3-yl]acetyl}-L-prolinamide;
or a salt thereof;

6) a prodrug of compound (I);

7) a pharmaceutical agent comprising compound (I) or a prodrug thereof;

8) the pharmaceutical agent of the aforementioned 7), which is an agent for the prophylaxis or treatment of diabetes, diabetic complications, impaired glucose tolerance or obesity;

9) a peptidase inhibitor comprising compound (I) or a prodrug thereof;

10) the inhibitor of the aforementioned 9), wherein the peptidase is dipeptidyl peptidase-IV;

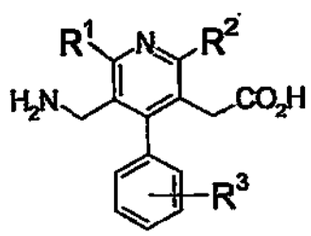
11) use of compound (I) or a prodrug thereof for the production of an agent for the prophylaxis or treatment of diabetes, diabetic complications, impaired glucose tolerance or obesity;

12) use of compound (I) or a prodrug thereof for the production of a peptidase inhibitor;

13) a method of preventing or treating diabetes, diabetic complications, impaired glucose tolerance or obesity in a mammal, which comprises administering compound (I) or a prodrug thereof to said mammal;

14) a method of inhibiting peptidase in a mammal, which comprises administering compound (I) or a prodrug thereof to said mammal;

15) a method of producing a compound represented by the formula (I-a):



I-a

wherein

R^1 is a C_{1-6} alkyl group optionally substituted by a C_{3-10} cycloalkyl group,

R^2 is a C_{2-6} alkyl group, and

R^3 is a hydrogen atom, a C_{1-6} alkyl group or a halogen atom, or a salt thereof, which comprises subjecting a compound represented by the formula (1):

1

wherein

P is a hydrogen atom or an amino-protecting group, and

R^1, R^2 and R^3 are each as defined above, or a salt thereof, to hydrolysis and deprotection;

and the like.

The compound of the present invention has a superior peptidase inhibitory action and is useful as an agent for the prophylaxis or treatment of diabetes and the like.

Best Mode for Embodying the Invention

Each symbol in the formula (I) is described in detail in the following.

As the "C_{1-6} alkyl group" of the "C_{1-6} alkyl group optionally substituted by a C_{3-10} cycloalkyl group" for R^1, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl and the like can be mentioned.

As the "C_{3-10} cycloalkyl group" of the "C_{1-6} alkyl group optionally substituted by a C_{3-10} cycloalkyl group" for R^1, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl,

bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.1]decyl, adamantyl and the like can be mentioned.

R^1 is preferably a C_{3-6} alkyl group, more preferably a branched C_{3-6} alkyl group, particularly preferably isobutyl or neopentyl.

As the "C_{2-6} alkyl group" for R^2, for example, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl and the like can be mentioned.

R^2 is preferably ethyl or isobutyl.

As the "C_{1-6} alkyl group" for R^3, those exemplified for the aforementioned R^1 can be mentioned.

As the "halogen atom" for R^3, for example, fluorine, chlorine, bromine and iodine can be mentioned.

R^3 is preferably a C_{1-6} alkyl group, more preferably methyl.

As the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for R^4, R^5 or R^6, for example, a C_{1-10} alkyl group, a C_{2-10} alkenyl group, a C_{2-10} alkynyl group, a C_{3-10} cycloalkyl group, a C_{3-10} cycloalkenyl group, a C_{4-10} cycloalkadienyl group, a C_{6-14} aryl group, a C_{7-13} aralkyl group, a C_{8-13} arylalkenyl group, a C_{3-10} cycloalkyl-C_{1-6} alkyl group and the like can be mentioned.

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

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

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

As the C_{3-10} cycloalkyl group, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.1]decyl, adamantyl and the like can be mentioned.

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

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

The above-mentioned C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group and C_{4-10} cycloalkadienyl group are each optionally condensed with a benzene ring, and, for example, indanyl, dihydronaphthyl, tetrahydronaphthyl, fluorenyl and the like can be mentioned.

As the C_{6-14} aryl group, for example, phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl, biphenylyl and the like can be mentioned. Of these, phenyl, 1-naphthyl, 2-naphthyl and the like are preferable.

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

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

As the C_{3-10} cycloalkyl-C_{1-6} alkyl group, for example, cyclohexylmethyl and the like can be mentioned.

The aforementioned C_{1-10} alkyl group, C_{2-10} alkenyl group and C_{2-10} alkynyl group optionally have 1 to 3 substituents at substitutable positions.

As such substituents, for example,

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

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

(3) an aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, oxazolyl, thiazolyl, tetrazolyl, oxadiazolyl, pyrazinyl, quinolyl, indolyl) optionally substituted by 1 to 3 substituents selected from a carboxyl group, a carbamoyl group, a thiocarbamoyl group and a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl);

(4) a non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidinyl, piperazinyl, oxodioxolyl, oxodioxolanyl, oxo-2-benzofuranyl, oxooxadiazolyl) optionally substituted by a C_{1-6} alkyl group (e.g., methyl, ethyl);

(5) an amino group optionally mono- or di-substituted by substituent(s) selected from a C_{1-6} alkyl group (e.g., methyl, ethyl), a C_{1-6} alkyl-carbonyl group (e.g., acetyl, isobutanoyl, isopentanoyl) and a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl);

(6) a C_{1-6} alkylsulfonylamino group (e.g., methylsulfonylamino);

(7) an amidino group;

(8) a C_{1-6} alkyl-carbonyl group (e.g., acetyl, isobutanoyl, isopentanoyl);

(9) a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl);

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

(11) a carbamoyl group optionally mono- or di-substituted by C_{1-6} alkyl group(s) (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

(12) a thiocarbamoyl group optionally mono- or di-substituted by C_{1-6} alkyl group(s) (e.g., methyl, ethyl) optionally substituted

by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

(13) a sulfamoyl group optionally mono- or di-substituted by C_{1-6} alkyl group(s) (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

(14) a carboxyl group;

(15) a hydroxy group;

(16) a C_{1-6} alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

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

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

(19) a C_{7-13} aralkyloxy group (e.g., benzyloxy);

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

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

(22) a thiol group;

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

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

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

(26) a sulfo group;

(27) a cyano group;

(28) an azido group;

(29) a nitro group;

(30) a nitroso group;

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

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

and the like can be mentioned.

The C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group, C_{4-10} cycloalkadienyl group, C_{6-14} aryl group, C_{7-13} aralkyl group, C_{8-13}

arylalkenyl group and C_{3-10} cycloalkyl-C_{1-6} alkyl group, which are exemplarily recited for the aforementioned "hydrocarbon group", optionally have 1 to 3 substituents at substitutable positions.

As such substituents, for example,
those exemplarily recited for the substituents for the aforementioned C_{1-10} alkyl group and the like;
a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a carboxyl group, a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl), a carbamoyl group and a C_{1-6} alkoxy group (e.g., methoxy);
a C_{2-6} alkenyl group (e.g., ethenyl, 1-propenyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a carboxyl group, a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl) and a carbamoyl group;
a C_{7-13} aralkyl group (e.g., benzyl);
an oxo group;
and the like can be mentioned.

As the "heterocyclic group" of the "optionally substituted heterocyclic group" for R^4, R^5 or R^6, an aromatic heterocyclic group and a non-aromatic heterocyclic group can be mentioned.

As the aromatic heterocyclic group, for example, a 5- to 7-membered monocyclic aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 heteroatoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and a fused aromatic heterocyclic group can be mentioned. As the fused aromatic heterocyclic group, for example, a group wherein these 5- to 7- membered monocyclic aromatic heterocyclic groups and a 6-membered ring containing 1 or 2 nitrogen atoms, a benzene ring or a 5-membered ring containing one sulfur atom are fused, and the like can be mentioned.

As preferable examples of the aromatic heterocyclic group,

monocyclic aromatic heterocyclic groups such as furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl, oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl) and the like;

fused aromatic heterocyclic groups such as quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl), benzofuryl (e.g., 2-benzofuryl, 3-benzofuryl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), benzothiadiazolyl (e.g., benzo[1,2,5]thiadiazol-4-yl), benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl), indolyl (e.g., indol-1-yl, indol-3-yl), indazolyl (e.g., 1H-indazol-3-yl), pyrrolopyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyrazin-6-yl), imidazopyridinyl (e.g., 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl) and the like,

and the like can be mentioned.

As the non-aromatic heterocyclic group, for example, a 5- to 7-membered monocyclic non-aromatic heterocyclic group

containing, as a ring-constituting atom besides carbon atoms, 1 to 4 heteroatoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and a fused non-aromatic heterocyclic group can be mentioned. As the fused non-aromatic heterocyclic group, for example, a group wherein these 5- to 7- membered monocyclic non-aromatic heterocyclic groups and a 6-membered ring containing 1 or 2 nitrogen atoms, a benzene ring or a 5-membered ring containing one sulfur atom are fused, and the like can be mentioned.

As preferable examples of the non-aromatic heterocyclic group, pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), piperidinyl (e.g., piperidino), morpholinyl (e.g., morpholino), thiomorpholinyl (e.g., thiomorpholino), piperazinyl (e.g., 1-piperazinyl), hexamethyleniminyl (e.g., hexamethylenimin-1-yl), oxazolidinyl (e.g., oxazolidin-3-yl), thiazolidinyl (e.g., thiazolidin-3-yl), imidazolidinyl (e.g., imidazolidin-3-yl), oxoimidazolidinyl (e.g., 2-oxoimidazolidin-1-yl), dioxoimidazolidinyl (e.g., 2,4-dioxoimidazolidin-3-yl), dioxooxazolidinyl (e.g., 2,4-dioxooxazolidin-3-yl, 2,4-dioxooxazolidin-5-yl, 2,4-dioxooxazolidin-1-yl), dioxothiazolidinyl (e.g., 2,4-dioxothiazolidin-3-yl, 2,4-dioxothiazolidin-5-yl), dioxoisoindolinyl (e.g., 1,3-dioxoisoindolin-2-yl), oxooxadiazolidinyl (e.g., 5-oxooxadiazolidin-3-yl), oxothiadiazolidinyl (e.g., 5-oxothiadiazolidin-3-yl), oxopiperazinyl (e.g., 3-oxopiperazin-1-yl), dioxopiperazinyl (e.g., 2,3-dioxopiperazin-1-yl, 2,5-dioxopiperazin-1-yl), oxodioxolyl (e.g., 2-oxo-1,3-dioxol-4-yl), oxodioxolanyl (e.g., 2-oxo-1,3-dioxolan-4-yl), 3-oxo-1,3-dihydro-2-benzofuranyl (e.g., 3-oxo-1,3-dihydro-2-benzofuran-1-yl), oxodihydrooxadiazolyl (e.g., 5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl), oxodihydropyrazolyl (e.g., 5-oxo-4,5-dihydro-1H-pyrazol-3-yl), 4-oxo-2-thioxo-1,3-thiazolidin-5-yl, 4-oxo-2-thioxo-1,3-oxazolidin-5-yl, tetrahydropyranyl (e.g., 4-tetrahydropyranyl), 4-oxo-4,5,6,7-tetrahydro-1-benzofuranyl

(e.g., 4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-yl), 1,3(2H,5H)-dioxotetrahydroimidazo[1,5-a]pyridinyl, 1,3(2H,5H)-dioxo-10,10a-dihydroimidazo[1,5-b]isoquinolinyl, azabicyclooctyl (e.g., 1-azabicyclo[2.2.2]octan-2-yl, 1-azabicyclo[2.2.2]octan-3-yl) and the like can be mentioned.

As the "nitrogen-containing heterocycle" of the "optionally substituted nitrogen-containing heterocycle" formed by R^4 and R^5 together with the adjacent nitrogen atom, for example, a 5- to 7-membered nitrogen-containing heterocycle containing, as a ring-constituting atom besides carbon atoms, at least one nitrogen atom and optionally further containing 1 or 2 heteroatoms selected from an oxygen atom, a sulfur atom and a nitrogen atom can be mentioned. As preferable examples of the "nitrogen-containing heterocycle", pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine, oxopiperazine, homopiperidine, homopiperazine, thiazolidine, dihydroindole (e.g., 2,3-dihydroindole), dihydroisoindole (e.g., 1,3-dihydroisoindole), tetrahydroquinoline (e.g., 1,2,3,4-tetrahydroquinoline), triazaspirodecanedione (e.g., 1,3,8-triazaspiro[4.5]decane-2,4-dione), hexahydropyrazinooxazinone (e.g., hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one) and the like can be mentioned.

The nitrogen-containing heterocycle optionally has 1 to 3 (preferably 1 or 2) substituents at substitutable positions. As such substituents, for example, those exemplarily recited for the substituents for the C_{3-10} cycloalkyl group, which is exemplarily recited for the aforementioned "hydrocarbon group" of the "optionally substituted hydrocarbon group" for R^4 or R^5, can be mentioned.

As the "optionally substituted hydroxy group" for R^5, for example, a hydroxy group optionally substituted by a hydrocarbon group can be mentioned.

As the hydrocarbon group, here, those exemplarily recited for the aforementioned "hydrocarbon group" of the "optionally

substituted hydrocarbon group" for R^4, R^5 or R^6 can be mentioned.

The "optionally substituted hydroxy group" is preferably a hydroxy group, a C_{1-6} alkoxy group (e.g., methoxy, ethoxy) and the like.

R^4 and R^5 are preferably the same or different and each is a hydrogen atom (only for R^4), an optionally substituted C_{1-10} alkyl group, an optionally substituted C_{3-10} cycloalkyl group, an optionally substituted C_{6-14} aryl group, an optionally substituted C_{7-13} aralkyl group, an optionally substituted heterocyclic group or an optionally substituted hydroxy group (only for R^5). To be specific,

(1) a hydrogen atom (only for R^4);

(2) a C_{1-10} alkyl group (preferably methyl, ethyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkoxy-carbonyl group, a C_{1-6} alkoxy group and a heterocyclic group (e.g., 2-thienyl);

(3) a C_{3-10} cycloalkyl group optionally condensed with a benzene ring (preferably indanyl, tetrahydronaphthyl);

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

(4a) a halogen atom;

(4b) a C_{1-6} alkyl group optionally substituted by a C_{1-6} alkoxy-carbonyl group;

(4c) a C_{1-6} alkyl-carbonyl group;

(4d) a C_{1-6} alkylsulfonyl group; and

(4e) a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

(5) a C_{7-13} aralkyl group (preferably benzyl) optionally substituted by 1 to 3 C_{1-6} alkylsulfonyl groups;

(6) a heterocyclic group (e.g., pyridyl, isoxazolyl, pyrazolyl, thiadiazolyl, benzothiadiazolyl, oxodihydropyrazolyl, azabicyclooctyl, pyrrolidinyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group, a C_{6-14} aryl group, a C_{7-13} aralkyl group and a C_{1-6} alkoxy-carbonyl group; and

(7) a C_{1-6} alkoxy group (only for R^5);

are preferable.

As the "nitrogen-containing heterocycle" of the "optionally substituted nitrogen-containing heterocycle" formed by R^4 and R^5 together with the adjacent nitrogen atom, for example, pyrrolidine, piperidine, piperazine, morpholine, homopiperidine, homopiperazine, thiazolidine, dihydroindole, dihydroisoindole, tetrahydroquinoline, triazaspirodecanedione, hexahydropyrazinooxazinone and the like are preferable.

As the substituents for the nitrogen-containing heterocycle,

(1) a carbamoyl group;

(2) a C_{1-6} alkyl-carbonyl group;

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

(4) a C_{1-6} alkylsulfonyl group;

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

(6) a non-aromatic heterocyclic group (e.g., pyrrolidinyl);

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

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

are preferable.

R^6 is preferably a hydrogen atom or an optionally substituted C_{1-10} alkyl group. As the substituents for the C_{1-10} alkyl group, a non-aromatic heterocyclic group (e.g., oxodioxolyl) optionally substituted by a C_{1-6} alkyl group can be mentioned. R^6 is particularly preferably a hydrogen atom.

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

[Compound A]

A compound wherein

R^1 is a C_{3-6} alkyl group (preferably isobutyl, neopentyl);

R^2 is a C_{2-6} alkyl group (preferably ethyl, isobutyl);