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51 CLASIFICACIÓN INTERNACIONAL **C07D 487/04-A61K 31/4188-A61P 29/00**

71 SOLICITANTE **TAJABE SEIYAJ CO , S.A.**

DOMICILIO **BOGOTÁ, D.C.**

74 APODERADO **HERNANDO CAVELIER FRANCO**

22 BOGOTÁ, D.C. **05 de Agosto de 2004**

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

①

SOLICITUD DE:

☒ Patente de Invención.

☐ Patente de Modelo de Utilidad.

☐ Capítulo I.

☒ Capítulo II.

②

SOLICITANTE
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③

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TP 1519

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Inhibidores de Adhesión Celular Mediada por Integrina $\alpha_L \beta_2$

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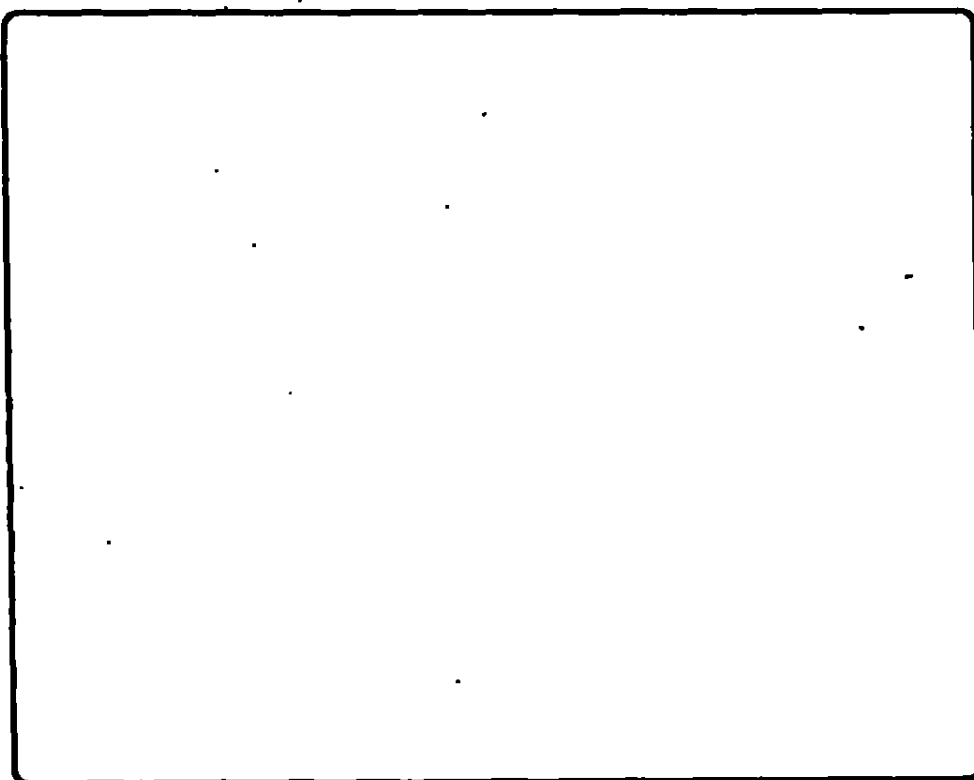
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Poderes, si fuere el caso.
- ☐ 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 indígenas.
- ☐ 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, relacionados parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☐ Otros

11 FIGURA CARACTERISTICA:



12

Solicito la concesión de la patente,

NOMBRE: Ernesto Cavalier-Franco

FIRMA: *Ernesto Cavalier*

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INHIBITORS OF $\alpha_L\beta_2$ INTEGRIN MEDIATED CELL ADHESION.

BACKGROUND OF THE INVENTION

5 Field of the Invention

The present invention relates to novel compounds that are potent inhibitors of $\alpha_L\beta_2$ integrin mediated cell adhesion which could be useful for the treatment of $\alpha_L\beta_2$ integrin mediated inflammatory conditions.

10

Description of Related Art

Leukocyte integrins and intercellular adhesion molecules (ICAMs) play pivotal roles in leukocyte adhesion to target cells and extracellular matrices. The β_2 (CD18) integrin subfamily has four members, each consisting of a related but distinct α -chain noncovalently paired with CD18: $\alpha_L\beta_2$ integrin (LFA-1, CD11a/CD18), $\alpha_M\beta_2$ integrin (Mac-1, CD11b/CD18), $\alpha_X\beta_2$ integrin (p150/95, CD11c/CD18), and $\alpha_D\beta_2$ integrin (CD11d/CD18) (Bochner ed., Adhesion Molecules in Allergic Disease, Marcel Dekker, Inc. pp 1-24 (1997)). Among them, LFA-1 has been shown to be central to the cell adhesion and transendothelial migration of T cells, eosinophils, and other leukocytes into inflamed tissues (Garmberg, Curr. Opin. Cell Biology, 9, 643-650 (1997); Panes et al., Br. J. Pharmacology, 126, 537-550 (1999)). LFA-1 binds to the ICAM family (ICAM-1, -2, -3, -4, -5) of molecules expressed on multiple cell types such as vascular endothelial cells, dendritic cells, epithelial cells, macrophage and T lymphoblasts (Dustin et al., J. Immunology, 137, 245-254 (1986)). In addition, LFA-1/ICAM-1 and LFA-1/ICAM-3 interactions can act as co-stimulatory signals required for T cell activation (Wingren et al., Crit. Rev. in Immunology, 15, 235-253 (1995)).

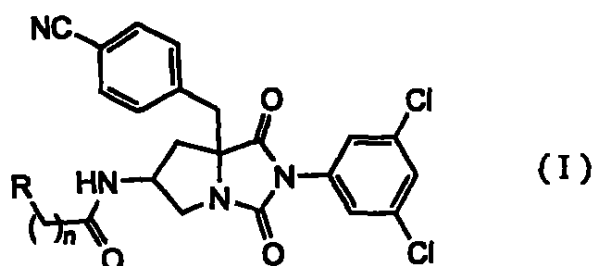
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Cell migration and T cell co-activation are important processes in a number of inflammatory disease states. A dominant role of LFA-1 in mediating inflammatory events is shown in several different animal models of inflammatory diseases in which antibodies to LFA-1 or ICAM-1 significantly inhibit development of therapeutic end points (Rothlein et al., Kidney International, 41, 617 (1992); Iigo et al., J. Immunology, 147, 4167 (1991); Bennet et al., J. Pharmacol. and Exp. Therapeutics, 280, 988 (1997)). In addition, a humanized monoclonal antibody to CD11a (the alpha chain of LFA-1) has shown efficacy in patients with psoriasis (Gottlieb et al., J. Am. Acad. Dermatology, 42, 428-35 (2000)).

Moreover, it has been shown that antibodies against LFA-1 suppress rejection after organ transplantation (Poston et al., Transplantation 69, 2005-2013 (2000); Nakakura et al. Transplantation 62, 547-552 (1996)). WO 94/04188 discloses the use of monoclonal antibodies directed against $\alpha_L\beta_2$ integrin for all transplantations.

20 SUMMARY OF THE INVENTION

The present invention relates to novel compounds of formula (I):



25 wherein R is hydrogen atom, hydroxyl group, or carbamoyl group, and n is 1 or 2, or a pharmaceutically acceptable salt thereof.

Detailed Description of the Invention

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The desired compounds of the present invention may exist in the form of optical isomers based on asymmetric atoms thereof, and the present invention also includes these optical isomers and mixtures thereof.

5 In an embodiment of the present invention, the steric configuration of a bond need not be fixed. The compounds of the present invention may be a compound with a sole configuration or a mixture with several different configurations.

10 In a preferred embodiment of the compounds of formula (I), R is hydrogen atom.

In another preferred embodiment of the compounds of formula (I), R is hydroxyl group.

In still another preferred embodiment of the compounds of
15 formula (I), R is carbamoyl group.

In a more preferred embodiment of the compounds of formula (I), n is 1.

In another more preferred embodiment of the compounds of formula (I), n is 2.

20 In a further preferred embodiment of the compounds of formula (I), R is hydrogen atom and n is 1.

In another further preferred embodiment of the compounds of formula (I), R is hydroxyl group and n is 1.

In still another further preferred embodiment of the
25 compounds of formula (I), R is carbamoyl group and n is 2.

Most preferred compounds of the present invention are selected from the following compounds:

(5S, 7S)-5-(4-Cyanobenzyl)-3-(3,5-dichlorophenyl)-7-acetylamino-1,3-diazabicyclo[3.3.0]octane-2,4-dione;

30 (5S, 7S)-5-(4-Cyanobenzyl)-3-(3,5-dichlorophenyl)-7-[(2-hydroxyacetyl)amino]-1,3-diazabicyclo[3.3.0]octane-2,4-dione;

(5S, 7S)-5-(4-Cyanobenzyl)-3-(3,5-dichlorophenyl)-7-[(3-carbamoylpropionyl)amino]-1,3-diazabicyclo[3.3.0]octane-2,4-dione.

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The characteristic of the present compounds is the combination of the acylamino group at 7-position and the 4-cyanobenzyl group at 5-position of 1,3-diazabicyclo[3.3.0]octane nucleus, where such characteristic is not specifically described in prior publications.

The compounds of the present invention have potent inhibitory activity against both LFA-1 mediated cell adhesion and LFA-1 mediated T cell co-activation, and also show excellent bioavailability after oral administration which reflects the overall improvement in (a) plasma protein binding, (b) aqueous solubility and (c) lipophilicity. The compounds of the present invention therefore show excellent in vivo efficacy against the unfavorable conditions caused by LFA-1 mediated cell adhesion.

In addition, the compounds of the present invention have potent antagonistic activity on substance P receptor, i.e., Neurokinin 1 (NK1) receptor, as well. Substance P receptor antagonists are considered to be useful for the treatment of inflammatory diseases such as asthma, rheumatoid arthritis, inflammatory bowel disease, cystitis, and other gastric disorders (Kraneveld et al., Int. Immunopharmacology, 1, 1629-1650 (2001); Swain et al., Ann. Rep. Med. Chem., 34, 51-60 (1999); Ohnmacht Jr. et al., Ann. Rep. Med. Chem., 33, 71-80 (1998)). Thus the compounds of the present invention has excellent therapeutic potential against the unfavorable conditions caused or mediated by substance P. Also, the compounds of the present invention may show excellent effects on the treatment or prevention of inflammatory diseases due to the dual activities of LFA-1 mediated cell adhesion inhibition and substance P receptor antagonism.

Moreover, the compounds of formula (I) have reduced cytotoxicity and low cytochrome P450 inhibitory activity as compared with those described previously, and therefore, the

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compounds of the present invention may have reduced side effect potential.

The compounds of the present invention may be clinically used either in a free form or in the form of pharmaceutically acceptable salts thereof. Pharmaceutically acceptable salts include an acid-addition salt with an inorganic acid or an organic acid, and a salt with an inorganic base, an organic base or an amino acid. Pharmaceutically acceptable salts also include an intramolecular salt thereof, or a solvate or
10 hydrate thereof.

The compounds of the present invention may be formulated into a pharmaceutical composition comprising a therapeutically effective amount of the compound as defined above and a pharmaceutically acceptable carrier or diluent. The
15 pharmaceutically acceptable carrier or diluent may be, for example, binders (e.g., syrup, gum arabic, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone), excipients (e.g., lactose, sucrose, corn starch, potassium phosphate, sorbitol, glycine), lubricants (e.g., magnesium stearate, talc, polyethylene
20 glycol, silica) disintegrators (e.g., potato starch), wetting agents (e.g., sodium laurylsulfate), and the like.

The desired compounds of the present invention or pharmaceutically acceptable salts thereof may be administered either orally or parenterally, and it may be used as a
25 suitable pharmaceutical preparation. These pharmaceutical preparations may be in the form of a solid preparation such as a tablet, a granule, a capsule, and a powder, or in the form of a liquid preparation such as solution, suspension, and emulsion, when administered orally. When administered
30 parenterally, the pharmaceutical preparation may be in the form of suppository, an injection preparation or an intravenous drip preparation using distilled water for injection, a physiological salt solution, an aqueous glucose

solution, and so on, and an inhalation by a conventional process.

The dose of the desired compounds of the present invention or pharmaceutically acceptable salts thereof vary
 5 depending on an administration method, age, sex, body weight, and condition of a patient, but, in general, the daily dose is preferably about 0.1 to 100 mg/kg/day, particularly preferably 1 to 100 mg/kg/day.

The compounds of the present invention can be used for
 10 treating or preventing LFA-1 mediated conditions in a patient, for example, a human patient. The compounds of the present invention can be also used for the treatment of a patient suffering from or susceptible to LFA-1 mediated conditions. Examples of LFA-1 mediated conditions include inflammatory
 15 diseases, autoimmune diseases, and allergic diseases.

The compounds of the present invention can also be used for the treatment or prevention of conditions caused or mediated by substance P in a patient, as well as for the treatment of a patient suffering from or susceptible to such
 20 conditions. Examples of the conditions may be inflammatory diseases.

The compounds of the present invention may be used for treatment or prevention of diseases such as rheumatoid arthritis, asthma, chronic obstructive pulmonary disease,
 25 allergy conditions, adult respiratory distress syndrome, AIDS, cardiovascular diseases, thrombosis, harmful platelet aggregation, reocclusion following thrombolysis, reperfusion injury, skin inflammatory diseases (e.g., psoriasis, eczema, contact dermatitis, atopic dermatitis), osteoporosis,
 30 osteoarthritis, atherosclerosis, arteriosclerosis including transplantation-associated arteriosclerosis, neoplastic diseases including metastasis of neoplastic or cancerous growth, wound, detaching retina, Type I diabetes, multiple sclerosis, systemic lupus erythematosus (SLE), ophthalmic

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inflammatory conditions, inflammatory bowel diseases (Crohn's disease and ulcerative colitis), cystitis, gastric disorder, regional enteritis, Sjogren's Syndrome, and other autoimmune diseases.

5 The compounds of the present invention may also be used for the rejection (i.e., chronic rejection and acute rejection) after organ transplantation, including allograft rejection (host vs. graft disease) and graft vs. host disease.

10 The compounds of the present invention may be preferably used for treatment or prevention of psoriasis, rheumatoid arthritis, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), systemic lupus erythematosus, atopic dermatitis, Sjogren's syndrome, and rejection after organ transplantation (allograft rejection and graft vs. host
15 disease).

20 The compounds of the present invention may be further preferably used for treatment or prevention of rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, psoriasis, multiple sclerosis, and rejection after organ transplantation.

 The compounds of the present invention may also be further preferably used for treatment or prevention of inflammatory diseases such as asthma, inflammatory bowel disease, cystitis and other gastric disorders.

25 According to the present invention, the desired compounds (I) can be prepared in accordance with one of the following methods:

Method A:

30 Among the compounds of the present invention, a compound of formula (I-a):


$$\text{H}-(\text{CH}_2)_n-\text{COOH} \quad (\text{III-a})$$

10 resulting compound into a pharmaceutically acceptable salt thereof, if desired.

15 inorganic base (e.g., an alkali metal salt such as a sodium salt or a potassium salt, an alkaline earth metal salt such as a barium salt or calcium salt).

20 carried out in the presence of a condensing reagent, with or without a base in a suitable solvent.

The condensing reagent can be selected from conventional condensing reagents which can be used for a peptide synthesis, for example, BOP-Cl, BOP reagent, DCC, EDC or CDI. The

condensing reagent can be preferably used with an activator (e.g., HOBT).

The base can be selected from conventional organic bases such as an alkylamine (e.g., DIEA, Et₃N), a cyclic amine (e.g., DBU, DBN, 4-methylmorpholine), and pyridines (e.g., pyridine, DMAP), and conventional inorganic bases such as an alkali metal carbonate (e.g., Na₂CO₃, K₂CO₃), an alkali metal hydrogen carbonate (e.g., NaHCO₃, KHCO₃), an alkali metal hydroxide (e.g., NaOH, KOH), and the like.

10 The solvent can be selected from any one which does not disturb the condensation reaction, for example, esters (e.g., methyl acetate, ethyl acetate), halogenoalkanes (e.g., CHCl₃, CH₂Cl₂), ethers (e.g., diethyl ether, THF, DME, dioxane), amides (e.g., DMF, N-methylpyrrolidone), ketones (e.g.,
15 acetone, methyl ethyl ketone), CH₃CN, DMSO, and H₂O, and a mixture of these solvents. The reaction can be carried out at a temperature of -50°C to 50°C, preferably from 0°C to room temperature.

The condensation reaction of compound (II) or a salt
20 thereof with the reactive derivative of compound (III-a) is carried out in the presence or absence of a base in a suitable solvent or without solvent.

Examples of the reactive derivative of the compound (III-a) are an acid halide (e.g., an acid chloride), a reactive
25 ester (e.g., an ester with p-nitrophenol), an anhydride thereof, a mixed anhydride with other carboxylic acid (e.g., a mixed anhydride with isobutyric acid), and the like.

The base can be selected from conventional organic bases such as an alkylamine (e.g., DIEA, Et₃N), a cyclic amine (e.g.,
30 DBU, DBN, 4-methylmorpholine), and pyridines (e.g., pyridine, DMAP), and conventional inorganic bases such as an alkali metal carbonate (e.g., Na₂CO₃, K₂CO₃), an alkali metal hydrogen carbonate (e.g., NaHCO₃, KHCO₃), an alkali metal hydroxide (e.g., NaOH, KOH), and the like.

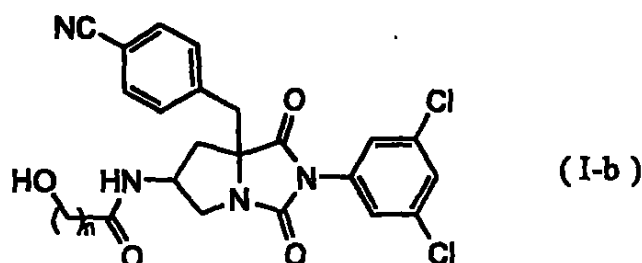
The solvent can be selected from any one which does not disturb the condensation reaction, for example, esters (e.g., methyl acetate, ethyl acetate), halogenoalkanes (e.g., CHCl_3 , CH_2Cl_2), ethers (e.g., diethyl ether, THF, dioxane), amides (e.g., DMF, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), CH_3CN , DMSO, and H_2O , and a mixture of these solvents.

The condensation reaction can be carried out at a temperature of -30°C to room temperature.

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Method B:

Among the compounds of the present invention, a compound of formula (I-b):



15 wherein n is the same as defined above, or a pharmaceutically acceptable salt thereof, can be prepared by condensing compound (II) or a salt thereof with a compound of formula (III-b):



20 wherein R^1O is a protected or unprotected hydroxyl group, and n is the same as defined above, a salt thereof, or a reactive derivative thereof, followed by removing the protecting group, and further converting the resulting compound into a pharmaceutically acceptable salt thereof, if necessary.

25 The salt of compound (III-b) may be, for example, a salt with an inorganic base (e.g., an alkali metal salt such as a sodium salt and a potassium salt, and an alkaline earth metal salt such as a barium salt and a calcium salt).

The protecting group for the hydroxyl group can be
30 selected from conventional protecting groups for a hydroxyl

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group which can be easily removed by a conventional method. Examples of such protecting groups include a trialkylsilyl group (e.g., trimethylsilyl group, triethylsilyl group, and t-butyltrimethylsilyl group), a benzyl group, a methyl group and
5 a tetrahydropyranyl group.

The condensation reaction of compound (II) or a salt thereof with compound (III-b) wherein R¹O is a protected hydroxyl group, a salt thereof or a reactive derivative thereof can be carried out in a similar procedure as described
10 in Method A.

The removal of the protecting group can be carried out by a usual method which is selected according to the protecting group to be removed, for example, hydrolysis, acid treatment, BBr₃ treatment, and catalytic reduction.

15 The hydrolysis can be carried out by using an inorganic base such as an alkali metal hydroxide (e.g., LiOH, NaOH, and KOH) in a suitable solvent such as ethers (e.g., diethyl ether, dioxane, and THF), alcohols (e.g., MeOH, EtOH), CH₃CN, DMSO, H₂O, and the like at room temperature or with heating.

20 The acid treatment can be carried out by using an inorganic acid or an organic acid such as hydrochloride, hydrobromide, acetic acid, p-toluenesulfonic acid, and trifluoroacetic acid in a suitable solvent such as ethers (e.g., diethyl ether, dioxane, THF), halogenoalkanes (e.g., CHCl₃, CH₂Cl₂), alcohols (e.g.,
25 MeOH, EtOH), CH₃CN, DMSO, H₂O, and the like at room temperature or with heating.

The catalytic reduction can be carried out by using a catalyst such as palladium on activated carbon and Raney-nickel under a hydrogen atmosphere at room temperature or with
30 heating in a suitable solvent such as ethers (e.g., diethyl ether, dioxane, THF), esters (e.g., methyl acetate, ethyl acetate), alcohols (e.g., MeOH, EtOH), CH₃CN, AcOH, H₂O, and the like.

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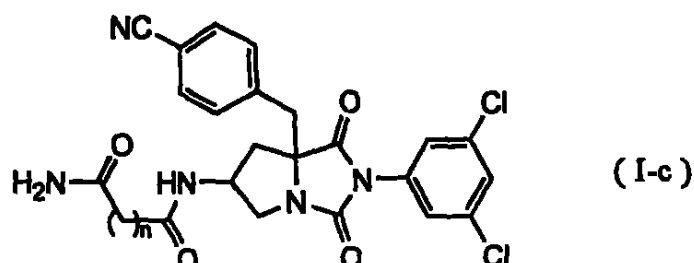
The treatment with BBr_3 for the demethylation can be carried out in a suitable solvent (e.g., THF, CH_2Cl_2 , AcOH) at a temperature of -78°C to 50°C .

In case that compound (III-b) wherein R^1O is a hydroxyl group is used for the condensation reaction, the hydroxyl group of compound (III-b) should be protected in situ prior to the condensation reaction.

The protection of the hydroxyl group can be carried out by reacting compound (III-b) with a trialkylsilyl halide in a suitable solvent with the presence of a base. Examples of the trialkylsilyl halide include trimethylsilyl chloride, triethylsilyl chloride, and t-butyldimethylsilyl chloride. The base can be selected from conventional bases which are used for the hydroxyl group protection, for example, triethylamine, imidazole, and pyridine. The solvent can be selected from any one which does not disturb the reaction, for example, esters (e.g., methyl acetate, ethyl acetate), aromatic hydrocarbons (e.g., benzene, toluene), halogenoalkanes (e.g., CHCl_3 , CH_2Cl_2), ethers (e.g., diethyl ether, THF, DME, dioxane), amides (e.g., DMF, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), CH_3CN , DMSO, and a mixture of these solvents. The reaction can be carried out at a temperature of -50°C to 50°C , preferably from 0°C to room temperature. The protected compound can be isolated in a usual procedure, if necessary.

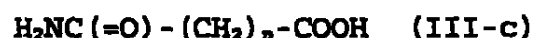
Method C:

Among the compounds of the present invention, a compound of formula (I-c):



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wherein n is the same as defined above, or pharmaceutically acceptable salt thereof, can be prepared by condensing compound (II) with a compound of formula (III-c):



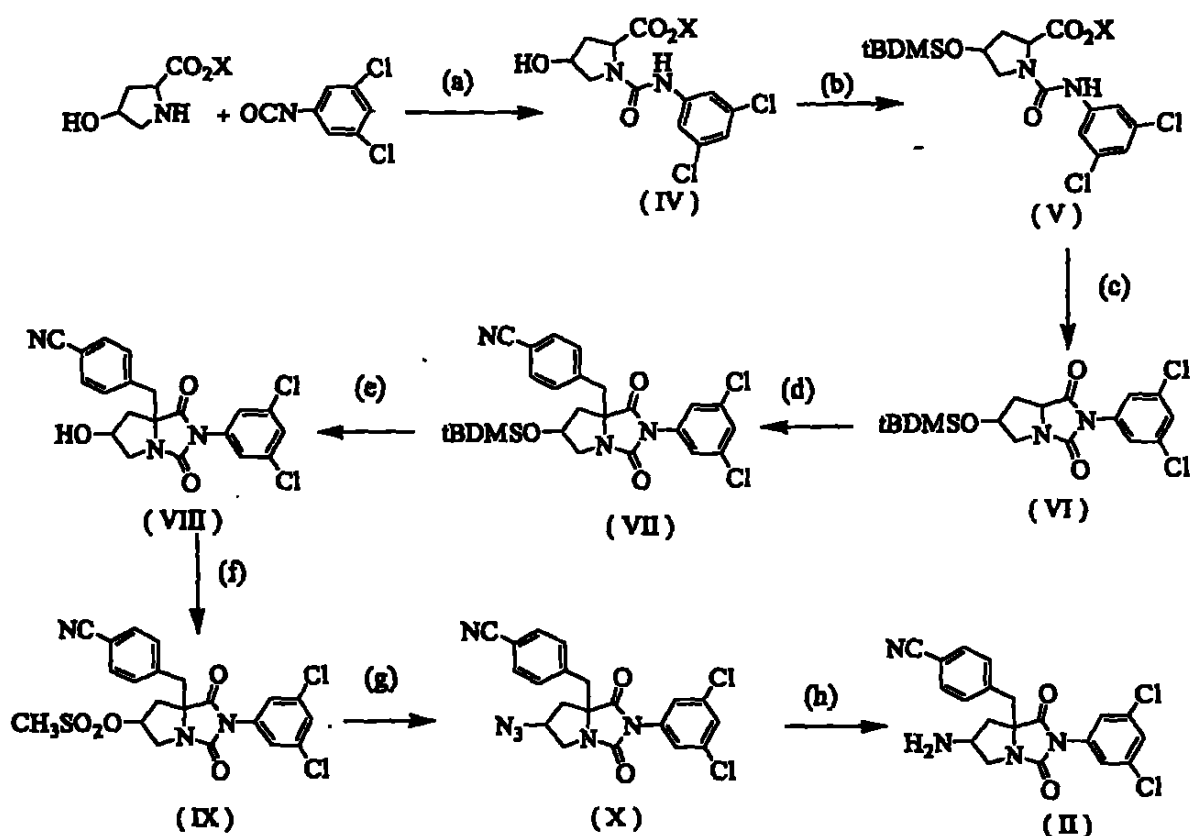
5 wherein n is the same as defined above, a salt thereof, or a reactive derivative thereof, followed by converting the resulting compound into a pharmaceutically acceptable salt thereof, if desired.

The salt of compounds (III-c) may be, for example, a salt
10 with an inorganic base (e.g., an alkali metal salt such as a sodium salt or a potassium salt, an alkaline earth metal salt such as a barium salt or a calcium salt).

The reaction of compound (II) or a salt thereof with compound (III-c) or a salt thereof can be carried out in a
15 similar method as described in Method A.

The starting compound of formula (II) can be prepared in accordance with the description of WO 01/30781 or the following scheme:

20 Scheme 1.



(In the above scheme, X is a C₁₋₆ alkyl group or a benzyl group, and tBDMSO is tert-butyldimethylsilyloxy group.)

5 Step (a): Compound (IV) can be prepared by reacting 4-hydroxyproline C₁₋₆ alkyl or benzyl ester with 3,5-dichlorophenylisocyanate in the presence of a base in a suitable solvent.

The base can be selected from conventional organic bases such as an alkylamine (e.g., Et₃N, DIEA) and pyridine, and conventional inorganic bases such as an alkali metal hydrocarbonate (e.g., NaHCO₃, KHCO₃) and an alkali metal carbonate (e.g., Na₂CO₃, K₂CO₃).

The solvent can be selected from any one which does not disturb the condensation reaction, for example, CH₂Cl₂, DME, THF, DMF, HMPA or a mixture thereof. The reaction can be carried out at a temperature of -78 °C to room temperature.

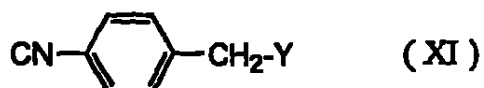
Step (b): Compound (V) can be prepared by protecting the hydroxyl group of compound (IV). The protection can be carried out by a usual manner, for example, by reacting compound (IV) with tert-butyldimethylsilyl chloride in the presence of
 5 imidazole in a suitable solvent such as CH₃CN. The reaction is carried out at a temperature of 0 °C to boiling point of the solvent, preferably at room temperature.

Step (c): Compound (VI) can be prepared by cyclizing compound
 10 (V). The cyclization can be carried out in the presence or absence of a base in a suitable solvent.

The base can be selected from conventional inorganic bases such as an alkali metal alkoxide (e.g., NaOEt, NaOMe), an alkali metal carbonate (e.g., K₂CO₃, Na₂CO₃) and an alkali
 15 metal hydrocarbonate (e.g., NaHCO₃), and conventional organic bases such as pyridine, DMAP, Et₃N, and DIEA.

The solvent can be selected from any one which does not disturb the cyclization reaction, for example, toluene, DME, CH₂Cl₂, THF, CH₃CN, DMF, alcohols (e.g., MeOH, EtOH) or a
 20 mixture thereof. The reaction is carried out at a temperature of 0 °C to boiling point of the solvent, preferably at 50 °C to 100 °C.

Step (d): Compound (VII) can be prepared by condensing
 25 compound (VI) with a compound of formula (XI):



wherein Y is a leaving group.

The leaving group may be selected from a halogen atom (e.g., a chlorine atom, a bromine atom, and an iodine atom),
 30 p-toluenesulfonyloxy group, and methanesulfonyloxy group.

The condensation reaction can be carried out in the presence of a base in a suitable solvent.

The base can be selected from conventional bases such as an alkali metal amide (e.g., LDA, KHMDS with or without LiCl).

The solvent can be selected from any one which does not disturb the condensation reaction, for example, diethyl ether, 5 DME, THF, DMF, HMPA or a mixture thereof. The reaction can be carried out at a temperature of -78 °C to room temperature.

Step (e): Compound (VIII) can be prepared by deprotecting compound (VII). The deprotection can be carried out by a usual 10 method, for example, treating the compound with HF/pyridine, n-Bu₄NF, or an acid (e.g., HCl, AcOH, TFA, p-TsOH) in a suitable solvent or without a solvent.

The solvent can be selected from any one which does not disturb the condensation reaction, for example, CH₃CN, THF, DMF 15 alcohols (e.g., MeOH, EtOH) or a mixture thereof. The reaction can be carried out at a temperature of -78 °C to room temperature.

Step (f): Compound (IX) can be prepared by reacting compound 20 (VIII) with methanesulfonyl chloride in the presence of a base in a suitable solvent.

The base can be selected from conventional bases such as Et₃N, DIEA, pyridine, NaHCO₃, KHCO₃, Na₂CO₃, K₂CO₃, and KHCO₃.

The solvent can be selected from any one which does not 25 disturb the reaction, for example, CH₂Cl₂, THF, DMF, CH₃CN, toluene. The reaction can be carried out at a temperature of -20 °C to 50 °C.

Step (g): Compound (X) can be prepared by reacting compound 30 (IX) with an alkali metal azide (e.g., NaN₃).

The substitution reaction can be carried out at a temperature of 0 °C to 100 °C in an organic solvent.

20

The solvent can be selected from any one which does not disturb the reaction, for example, CH_2Cl_2 , THF, DMF, CH_3CN , and toluene.

5 Step (h): Compound (II) can be prepared by reducing compound (X). The reduction can be carried out under catalytic hydrogenation conditions, for example, in the presence of a Pd or Pt catalyst (e.g., Pd-C, PtO_2) in a suitable solvent under a H_2 atmosphere at room temperature.

10 The solvent can be selected from any one which does not disturb the reaction, for example, EtOAc, MeOH, and EtOH.

In the present description and the claims, the C_{1-6} alkyl group means a straight chain or branched chain alkyl group
15 having 1 to 6 carbon atoms, for example, methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, etc., preferably one having 1 to 4 carbon atoms.

Abbreviations

- 20 AcOEt: Ethyl acetate (=EtOAc)
AcOH: Acetic acid
BOP-Cl: Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BOP reagent: Benzotriazol-1-yloxy-
tris(dimethylamino)phosphonium hexafluorophosphate
25 BSA: Bovine serum albumin
CDI: Carbonyldiimidazole
DBN: 1,5-Diazabicyclo[4.3.0]non-5-ene
DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC: 1,3-Dicyclohexylcarbodiimide
30 DIEA: Diisopropylethylamine
DMAP: 4-Dimethylaminopyridine
DME: Dimethoxyethane
DMF: Dimethyl formamide
DMSO: Dimethyl sulfoxide

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- EDC: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
hydrochloride
- Et: Ethyl
- EtOH: Ethanol
- 5 HBSS: Hank's balanced salt solution
- HMPA: Hexamethylphosphoramide
- HOBT: 1-Hydroxybenzotriazole hydrate
- HSA: Human serum albumin
- KHMDS: Potassium hexamethyldisilazide (=Potassium
10 bis(trimethylsilyl)amide)
- LDA: Lithium diisopropylamide
- Me: Methyl
- MeOH: Methanol
- n-Bu: n-Butyl
- 15 tBDMS: tert-Butyldimethylsilyl
- THF: Tetrahydrofuran
- TFA: Trifluoroacetic acid
- p-TsOH: p-toluenesulfonic acid

20 Examples

The compounds of the present invention are exemplified by the following examples but not limited thereby.

Example 1. (5S, 7S)-5-(4-Cyanobenzyl)-3-(3,5-dichlorophenyl)-
25 7-acetylamino-1,3-diazabicyclo[3.3.0]octane-2,4-dione

To a solution of (5S, 7S)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-amino-1,3-diazabicyclo[3.3.0]octane-2,4-dione (78.5 mg) in THF (5 mL) was added acetic anhydride (1.0
30 mL). The reaction mixture was stirred for 2 hours at 45 °C, and the mixture was concentrated and purified by preparative thin-layer chromatography (silica gel; CH₂Cl₂) to afford the titled compound (84 mg). MS (m/z) 478.8 (MNa⁺).

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Example 2. (5S, 7S)-5-(4-Cyanobenzyl)-3-(3,5-dichlorophenyl)-7-[(3-carbamoylpropionyl)amino]-1,3-diazabicyclo[3.3.0]octane-2,4-dione

5 A mixture of (5S, 7S)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-amino-1,3-diazabicyclo[3.3.0]octane-2,4-dione (82.7 mg), succinamic acid (45.86 mg), EDC (93.12 mg), HOBT (61.24 mg) and DIEA (104.79 μ L) in THF (5 mL) was stirred overnight at room temperature. The reaction mixture was
10 concentrated and purified by high performance liquid chromatography (HPLC) (Beckman 5 μ C18 column; eluted with a gradient of H₂O/MeCN (10-100%)/0.1% TFA) to give 72 mg of the titled compound. MS (m/z) 536 (MNa⁺).

15 Example 3. (5S, 7S)-5-(4-Cyanobenzyl)-3-(3,5-dichlorophenyl)-7-[(2-carbamoylacetyl)amino]-1,3-diazabicyclo[3.3.0]octane-2,4-dione

A mixture of (5S, 7S)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-amino-1,3-diazabicyclo[3.3.0]octane-2,4-dione (200 mg), malonamic acid (59.5 mg), EDC (112 mg), HOBT (97.5 mg) and DIEA (168 μ L) in THF (5 mL) was stirred overnight at room temperature. The reaction mixture was evaporated. The residue was dissolved in EtOAc and the
25 resulting solution was washed with water, saturated aqueous NaHCO₃ solution, brine, dried (Na₂SO₄) and concentrated to give 212 mg of the titled compound. MS (m/z) 500 (MH⁺).

Example 4. (5S, 7S)-5-(4-Cyanobenzyl)-3-(3,5-dichlorophenyl)-7-[(3-hydroxypropionyl)amino]-1,3-diazabicyclo[3.3.0]octane-2,4-dione
30

Step 1: A mixture of (5S, 7S)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-amino-1,3-diazabicyclo[3.3.0]octane-2,4-

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di ne (0.300 g), 3-methoxypropionic acid (0.209 μ L), EDC (0.224 g), HOBT (0.221 g) and DIEA (0.38 μ L) in THF (15 mL) was stirred overnight at room temperature. The reaction mixture was evaporated. The residue was purified by HPLC

5 [Beckman 5 μ C18 column; eluted with a gradient of H₂O/MeCN (10-100%)/0.1% AcOH] to give a foam. It was dissolved in EtOAc and the resulting solution was washed with water, saturated aqueous NaHCO₃ solution, brine, dried (Na₂SO₄) and concentrated to give 0.259 g of (5S, 7S)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-[(3-methoxypropionyl)amino]-1,3-diazabicyclo[3.3.0]octane-2,4-dione. MS (m/z) 501 (MH⁺).

Step 2: BBr₃ (3 mL, 1M in CH₂Cl₂) was added to a solution of (5S, 7S)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-[(3-methoxypropionyl)amino]-1,3-diazabicyclo[3.3.0]octane-2,4-dione (0.16 g) in CH₂Cl (15 mL) at -78 °C and the mixture was stirred for 8 hours at -78 °C. The mixture was evaporated, and the residue was purified by HPLC (Beckman 5 μ C18 column; eluted with a gradient of H₂O/MeCN (10-100%)/0.1% AcOH) to give 20 foam. It was dissolved in EtOAc and the resulting solution was washed with water, saturated aqueous NaHCO₃ solution, brine, dried (Na₂SO₄) and concentrated to give 0.119 g of the titled compound. MS (m/z) 487 (MH⁺).

25 Example 5. (5S, 7S)-5-(4-Cyanobenzyl)-3-(3,5-dichlorophenyl)-7-[(2-hydroxyacetyl)amino]-1,3-diazabicyclo[3.3.0]octane-2,4-dione

Step 1: To a solution of (5S, 7S)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-amino-1,3-diazabicyclo[3.3.0]octane-2,4-dione (150 mg) and DIEA (189 μ L) in THF (4 mL) was added a solution of benzyloxyacetyl chloride (57 μ L) in THF (2 mL) and the mixture was stirred overnight at room temperature. The

reaction mixture was concentrated and the residue was taken up in EtOAc. The resulting solution was washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by HPLC (Beckman 5 μ C18 column; eluted with a gradient of 5 $\text{H}_2\text{O}/\text{MeCN}$ (10-100%)/0.1% AcOH) to give a foam. It was dissolved in EtOAc and the resulting solution was washed with water, saturated aqueous NaHCO_3 solution, brine, dried (Na_2SO_4) and concentrated to give 0.135 g of (5S, 7S)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-[(2-benzyloxyacetyl)amino]-1,3-diazabicyclo[3.3.0]octane-2,4-dione. MS (m/z) 563.4 [MH^+].

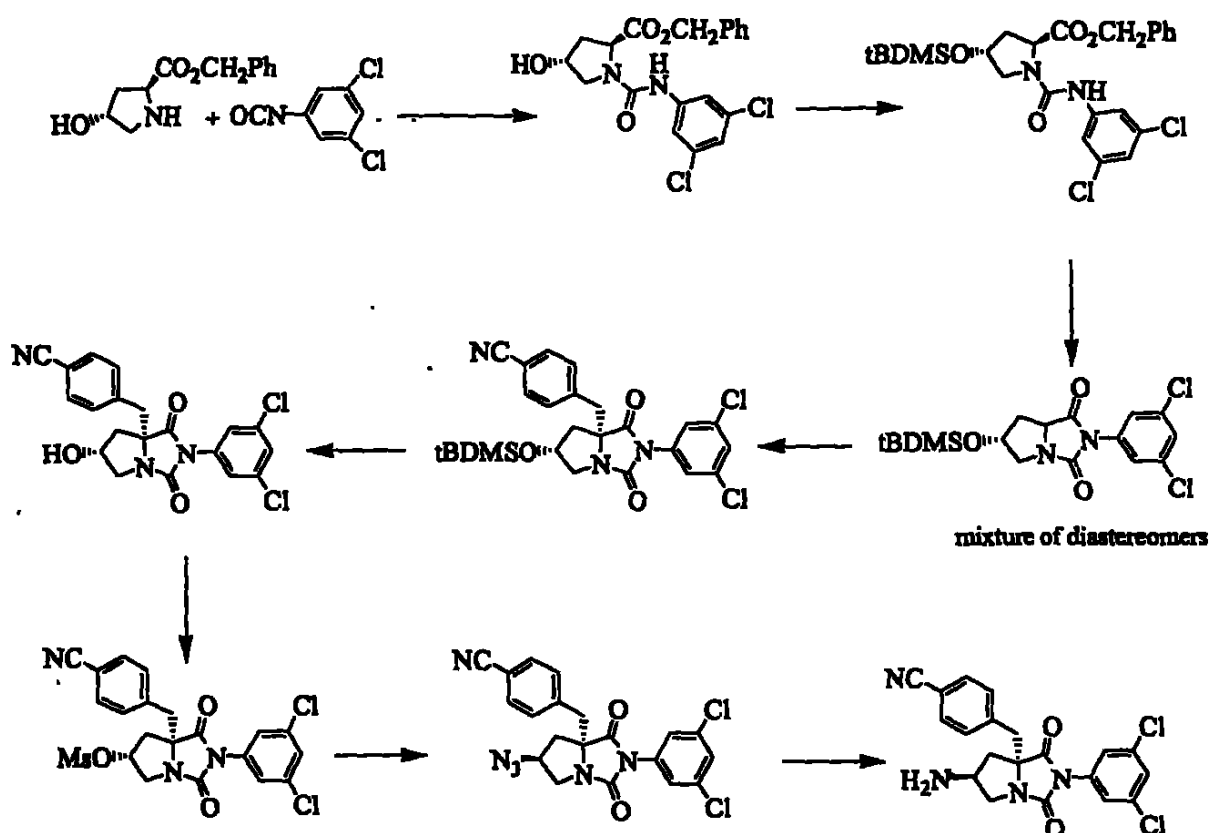
Step 2: Hydrogen was bubbled through a solution of (5S, 7S)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-[(2-benzyloxyacetyl)amino]-1,3-diazabicyclo[3.3.0]octane-2,4-dione from step 1 (0.125 g) in EtOH (10 mL) containing Pd/C (5%, 15 mg) and the reaction mixture was stirred overnight under a H_2 atmosphere. The mixture was recharged with additional 5% Pd/C (10 mg) and stirred overnight under a H_2 atmosphere. The reaction mixture was filtered through a bed of Celite and the filtrate was concentrated. The residue was purified by HPLC (Beckman 5 μ C18 column; eluted with a gradient of $\text{H}_2\text{O}/\text{MeCN}$ (10-100%)/0.1% TFA) to give 0.023 g of the titled compound. MS (m/z) 473 [MH^+] and 495 [MNa^+].

25

Reference Example 1: (5S, 7S)-5-(4-Cyanobenzyl)-3-(3,5-dichlorophenyl)-7-amino-1,3-diazabicyclo[3.3.0]octane-2,4-dione

30 The titled compound was prepared in accordance with the following scheme:

Scheme 2



5 Step-1: p-Toluene sulfonic acid (50.6 g) was added to a suspension of L-4-trans-hydroxyproline (25.25 g) in a mixture of benzyl alcohol (100 mL) and benzene (250 mL) and the mixture was heated under a Dean Stark trap for 24 hours. The reaction mixture was concentrated and diethyl ether was added
10 to precipitate the solid. The solid was filtered, washed with additional diethyl ether and dried to yield 75 g of L-4-trans-hydroxyproline benzyl ester.

Step-2: To a suspension of L-4-trans-hydroxyproline benzyl
15 ester p-toluene sulfonic acid salt from step 1 (40.43 g) in THF (500 mL) and DIEA (51.3 mL) was added 3,5-dichlorophenylisocyanate (22.1 g). After stirring overnight, the reaction mixture was concentrated. The residue was dissolved in EtOAc, washed with 0.5 N HCl, saturated aqueous

NaHCO₃ solution, brine, dried (Na₂SO₄), filtered and concentrated. The residue was triturated in EtOAc/hexane (1:1) and the white solid was filtered and purified via flash column chromatography (silica gel; hexane/EtOAc 2:1) to yield 5 (2S, 4R)-2-[(3,5-dichlorophenyl)carbamoyl]-4-hydroxyproline benzyl ester (33.07 g).

Step-3: To a suspension of (2S, 4R)-2-[(3,5-dichlorophenyl)carbamoyl]-4-hydroxyproline benzyl ester (33.07 10 g) in CH₃CN (800 mL) was added imidazole (11 g) and tert-butyldimethylsilyl chloride (13.64 g). After stirring for 48 hours, the reaction mixture was concentrated. The residue was dissolved in EtOAc, washed with 0.5 N HCl, saturated aqueous NaHCO₃ solution, brine, dried (Na₂SO₄), filtered and 15 concentrated. The residue was purified via flash column chromatography (silica gel; hexane/EtOAc 2:1) to give (2S, 4R)-2-[(3,5-dichlorophenyl)carbamoyl]-4-(tert-butyldimethylsilyloxy)proline benzyl ester (44.45 g).

20 Step-4: To a solution of the (2S, 4R)-2-[(3,5-dichlorophenyl)carbamoyl]-4-(tert-butyldimethylsilyloxy)proline benzyl ester (23.49 g) in CH₃CN (500 mL) was added DIEA (34.44 mL) and the mixture was heated to reflux. After refluxing for 24 hours the reaction mixture 25 was concentrated and purified by flash column chromatography (silica gel; hexane to hexane/EtOAc 1:1) to separate the two diastereomers of 3-(3,5-dichlorophenyl)-7-(tert-butyldimethylsilyloxy)-1,3-diazabicyclo[3.3.0]octane-2,4-dione. Diastereomer A: 7.46 g, MS: m/z 415 (M⁺); and 30 Diastereomer B: 10.66 g, MS: m/z 415 (M⁺).

Step-5: The compound from step 4, diastereomer A or B, (12.73 g) was benzylated as follows. n-Butyl lithium (30 mL, 1.6 M in hexane) was added with stirring to a solution of di-

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isopropylamine (6.5 mL) in THF (100 mL) at -78 °C under a N₂ atmosphere. The mixture was maintained at that temperature for additional 30 minutes. The mixture was added via cannula to a solution of 3-(3,5-dichlorophenyl)-7-(tert-butyl-
5 butyldimethylsilyloxy)-1,3-diazabicyclo[3.3.0]octane-2,4-dione (12.73 g) in dry THF (100 mL) at -78 °C under a N₂ atmosphere. After stirring at -78 °C for 30 minutes, 4-cyano- α -bromotoluene (9.08 g) in THF (100 mL) was added. The reaction mixture was stirred at -78 °C for 2.5 hours, then slowly warmed up to room
10 temperature and allowed to stand at room temperature for 0.5 hour. The reaction mixture was concentrated and the residue was dissolved in EtOAc. The EtOAc solution was washed with 0.5 N HCl, saturated aqueous NaHCO₃ solution, brine, dried (Na₂SO₄), filtered and concentrated. The residue was purified
15 via flash column chromatography (silica gel; hexane/EtOAc 24:1 to 3:1) to give (5S, 7R)- and (5R, 7R)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-(tert-butyl-
diazabicyclo[3.3.0]octane-2,4-dione.
(5S, 7R) isomer: 7.6 g, MS: m/z 530 (M⁺); and
20 (5R, 7R) isomer: 1.8 g, MS: m/z 530 (M⁺)

Step-6: To a solution of (5S, 7R)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-(tert-butyl-
diazabicyclo[3.3.0]octane-2,4-dione (1.0 g) in THF (1 mL) was
25 added 70% HF/pyridine (25 mL). The reaction mixture was stirred for 24 hours and then evaporated. The residue was dissolved in EtOAc and the resulting solution was washed with water, saturated aqueous NaHCO₃ solution, brine, dried (Na₂SO₄) and concentrated. The residue was purified by flash column
30 chromatography (silica gel; MeOH/CH₂Cl₂ 2-7%) to give (5S, 7R)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-hydroxy-1,3-diazabicyclo[3.3.0]octane-2,4-dione (0.52 g). MS (m/z) 416 [MH⁺].

Step 7: To a solution of (5S, 7R)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-hydroxy-1,3-diazabicyclo[3.3.0]octane-2,4-dione from step 6 (0.52 g) in CH₂Cl₂ (8 mL) at 0 °C was added DIEA (0.45 mL) followed by methanesulfonyl chloride (0.15 mL) 5 and the mixture stirred for 1.5 hours. The reaction mixture was diluted with CH₂Cl₂ and the resulting mixture was washed with saturated aqueous NaHCO₃ solution followed by brine, dried (Na₂SO₄), filtered and concentrated to give 0.76 g of (5S, 7R)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-methanesulfonyloxy-1,3-diazabicyclo[3.3.0]octane-2,4-dione. This compound was 10 used as is for the next step. MS (m/z) 501 [MH⁺].

Step 8: NaN₃ was added to a solution of (5S, 7R)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-methanesulfonyloxy-1,3-diazabicyclo[3.3.0]octane-2,4-dione from step 7 (0.76 g) in 15 DMF (5 mL) and the mixture was stirred for 24 hours. The reaction mixture was partitioned between EtOAc and water. The organic solution was washed with brine, dried (Na₂SO₄), filtered and concentrated. The residue was purified by flash 20 column chromatography (silica gel; CH₂Cl₂) to give 0.46 g of (5S, 7S)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-azido-1,3-diazabicyclo[3.3.0]octane-2,4-dione. MS (m/z) 441 [MH⁺].

Step 9: Hydrogen was bubbled through a solution of (5S, 7S)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-azido-1,3-diazabicyclo[3.3.0]octane-2,4-dione from step 8 (0.42 g) in 25 EtOH (15 mL) containing Pd/C (5%, 15 mg) and the reaction mixture was stirred overnight under a H₂ atmosphere. The reaction mixture was filtered through a bed of Celite and the 30 filtrate was concentrated. The residue was purified by HPLC (Beckman 5 μ C18 column; eluted with a gradient of H₂O/MeCN (10-100%)/0.1% TFA) to give 0.21 g of (5S, 7S)-5-(4-cyanobenzyl)-3-(3,5-dichlorophenyl)-7-amino-1,3-diazabicyclo[3.3.0]octane-2,4-dione. MS (m/z) 415 [MH⁺].

Reference Example 2: (5S, 7S)-5-(4-Cyanobenzyl)-3-(3,5-dichlorophenyl)-7-amino-1,3-diazabicyclo[3.3.0]octane-2,4-dione

5

Step 1: 3-(3,5-Dichlorophenyl)-7-(tert-butyldimethylsilyloxy)-1,3-diazabicyclo[3.3.0]octane-2,4-dione was prepared by following similar procedures as described in Reference Example 1, steps 1 through 4, but replacing L-4-
10 trans-hydroxyproline benzyl ester p-toluene sulfonic acid salt with L-4-trans-hydroxyproline methyl ester hydrochloride.

Step 2: 3-(3,5-Dichlorophenyl)-7-(tert-butyldimethylsilyloxy)-1,3-diazabicyclo[3.3.0]octane-2,4-dione from step 1 was
15 treated in similar procedures as described in Reference Example 1, steps 5 through 9 to afford the titled compound.

Cell Adhesion Protocol

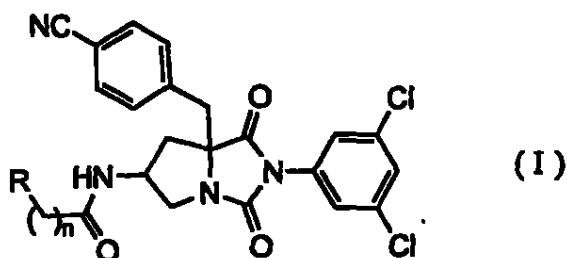
Cell Adhesion The recombinant protein ICAM-1•Fc was
20 constructed from the 5 extracellular domains of human ICAM-1 and fusion with the constant region of human IgG. ICAM-1•Fc was purified by Protein A affinity chromatography and stored in aliquots at -20°C. Immobilized ICAM-1•Fc was prepared by dilution of the protein in PBS pH 7.5, transfer of 100 µl/well
25 to Falcon Probind III plates and overnight incubation at 4°C. Wells coated with BSA served as a measure of non-specific background adhesion. Washed plates were blocked with a solution of 0.25% ovalbumin in PBS for 1 h at 37°C. HBSS washed Jurkat cells were suspended to a final concentration of
30 2.5×10^6 /ml in TBSg adhesion buffer (24 mM Tris pH 7.4, 0.14 M NaCl, 2.7 mM KCl, 2 mM glucose, 0.1% HSA). A 100 µl volume of cells was added to the blocked and washed ICAM-1•Fc coated plates that contained 100 µl of plate buffer (TBSg, 10 mM MgCl₂, 2% DMSO). Adhesion was for 1 h at 37°C. Non-adherent cells

were removed using the EL404 plate washer (BioTek Instruments; Highland Park, VT). The number of adherent cells was quantified by measuring enzymatic activity of endogenous N-acetyl-hexosaminidase using the enzyme substrate p-

5 nitrophenol-N-acetyl- β -D-glucoseaminide, pNAG. The amount of liberated p-nitrophenol was measured by reading the optical density at 405 nm using a vertical pathway spectrophotometer to quantify cell attachment (VMAX Kinetic Microplate Reader, Molecular Devices, Menlo Park, CA). For competition studies
10 th compounds from 100% DMSO stock solutions were diluted in plate buffer at 2-fold the required testing concentration prior to transfer to the ICAM-1-Fc coated plate and serial dilution.

Claims

1. A compound of the formula (I):



5 wherein R is hydrogen atom, hydroxyl group or carbamoyl group,
and n is 1 or 2, or a pharmaceutically acceptable salt thereof.

2. The compound or salt according to claim 1, wherein R is
hydrogen atom.

10

3. The compound or salt according to claim 1, wherein R is
hydroxyl group.

4. The compound or salt according to claim 1, wherein R is
15 carbamoyl group.

5. The compound or salt according to any one of claims 1-4,
wherein n is 1.

20 6. The compound or salt according to any one of claims 1-4,
wherein n is 2.

7. The compound or salt according to claim 1, wherein R is
hydrogen atom and n is 1.

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8. The compound or salt according to claim 1, wherein R is
hydroxyl group and n is 1.

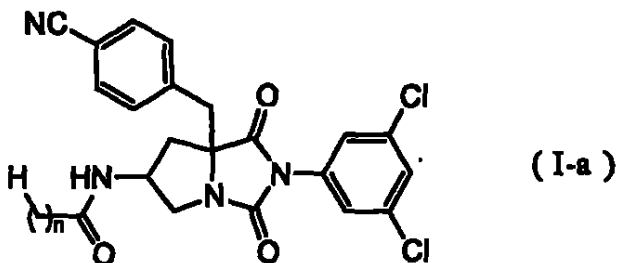
9. The compound or salt according to claim 1, wherein R is
30 carbamoyl group and n is 2.

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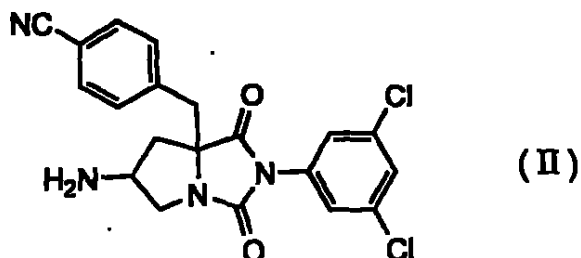
10. The compound or salt according to claim 1, wherein the compound is selected from the following compounds:

- (5S, 7S)-5-(4-Cyanobenzyl)-3-(3,5-dichlorophenyl)-7-acetylamino-1,3-diazabicyclo[3.3.0]octane-2,4-dione,
(5S, 7S)-5-(4-Cyanobenzyl)-3-(3,5-dichlorophenyl)-7-[(2-hydroxyacetyl)amino]-1,3-diazabicyclo[3.3.0]octane-2,4-dione,
(5S, 7S)-5-(4-Cyanobenzyl)-3-(3,5-dichlorophenyl)-7-[(3-carbamoylpropionyl)amino]-1,3-diazabicyclo[3.3.0]octane-2,4-dione.

11. A process for preparing a compound of formula (I-a):



wherein n is 1 or 2, or a pharmaceutically acceptable salt thereof, which comprises condensing a compound of formula (II):

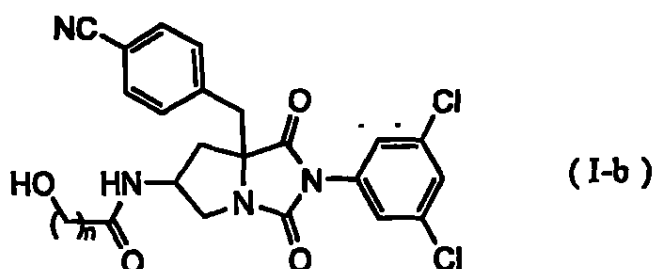


or a salt thereof, with a compound of formula (III-a):

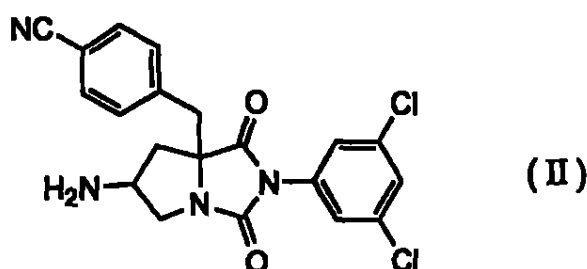


wherein n is the same as defined above, a salt thereof or a reactive derivative thereof, followed by converting the resulting compound into a pharmaceutically acceptable salt thereof, if desired.

12. A process for preparing a compound of formula (I-b):



wherein n is 1 or 2, or a pharmaceutically acceptable salt thereof, which comprises condensing a compound of formula (II):



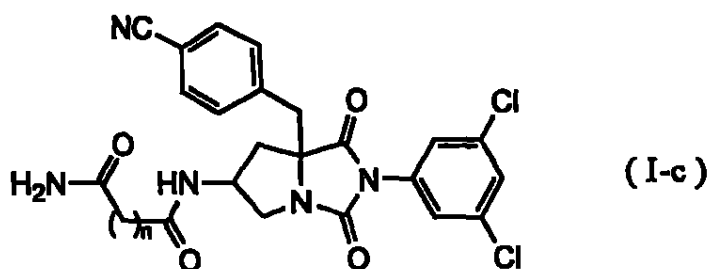
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or a salt thereof, with a compound of formula (III-b):



wherein R^1O is a protected or unprotected hydroxyl group, and n is the same as defined above, a salt thereof or a reactive
10 derivative thereof, followed by removing the protecting group, and further converting the resulting compound into a pharmaceutically acceptable salt thereof, if necessary.

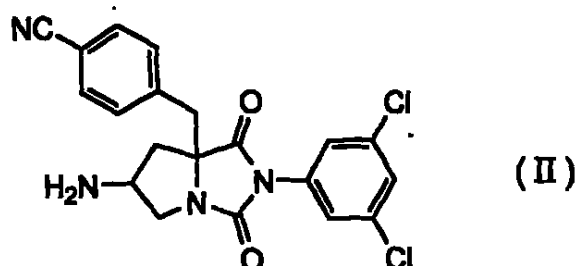
13. A process for preparing a compound of formula (I-c):



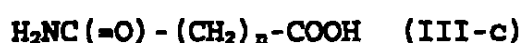
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wherein n is 1 or 2, or a pharmaceutically acceptable salt thereof, which comprises condensing a compound of formula (II)

34



or a salt thereof, with a compound of formula (III-c):



wherein n is the same as defined above, a salt thereof or a
5 reactive derivative thereof, followed by converting the
resulting compound into a pharmaceutically acceptable salt
thereof, if desired.

14. A pharmaceutical composition which comprises a
10 therapeutically effective amount of the compound or salt as
set forth in any one of claims 1-10 in admixture with a
therapeutically acceptable carrier or diluent.

15. A method for treatment or prevention of a LFA-1 mediated
15 condition in a patient comprising administering a
therapeutically effective amount of the compound or salt as
set forth in any one of claims 1-10.

16. The method according to claim 15, wherein the condition
20 is selected from an inflammatory disease, an autoimmune
disease, and an allergic disease.

17. A method for treatment or prevention of a condition
caused or mediated by substance P in a patient comprising
25 administering a therapeutically effective amount of the
compound or salt as set forth in any one of claims 1-10.

18. The method according to claim 17, wherein the condition
is an inflammatory disease.

35

19. A method for treatment or prevention of a condition in a patient comprising administering a therapeutically effective amount of the compound or salt as set forth in any one of claims 1-10, wherein said condition is selected from
5 rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, allergy conditions, adult respiratory distress syndrome, AIDS, cardiovascular diseases, thrombosis, harmful platelet aggregation, reocclusion following thrombolysis, reperfusion injury, skin inflammatory diseases, osteoporosis,
10 osteoarthritis, atherosclerosis, arteriosclerosis, neoplastic diseases, wound, detaching retina, Type I diabetes, multiple sclerosis, systemic lupus erythematosus, ophthalmic inflammatory conditions, inflammatory bowel diseases, cystitis, gastric disorder, regional enteritis, Sjogren's Syndrome, and
15 rejection after organ transplantation.

20. The method according to claim 19, wherein said condition is selected from psoriasis, rheumatoid arthritis, inflammatory bowel diseases, systemic lupus erythematosus, atopic
20 dermatitis, Sjogren's Syndrome, and rejection after organ transplantation.

21. The method according to claim 19, wherein said condition is selected from rheumatoid arthritis, asthma, chronic
25 obstructive pulmonary disease, psoriasis, multiple sclerosis, and rejection after organ transplantation.

22. The method according to claim 19, wherein said condition is selected from asthma, inflammatory bowel disease, cystitis,
30 and gastric disorder.

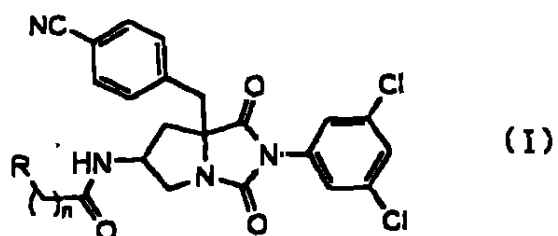
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INHIBIDORES DE LA ADHESIÓN CELULAR MEDIADA POR INTEGRINA $\alpha_1\beta_2$

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RESUMEN

La presente invención se refiere a un compuesto de fórmula (I):



en la cual R es un átomo de hidrógeno, un grupo hidroxilo o un grupo carbamoilo, y n es 1 o 2, o una sal farmacéuticamente aceptable del mismo.

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ANTECEDENTES DE LA INVENCION

Campo de la Invención

La presente invención se refiere a unos compuestos novedosos que son inhibidores potentes de la adhesión celular mediada por integrina $\alpha_L\beta_2$ que podrían ser útiles para el tratamiento de condiciones inflamatorias mediadas por integrina $\alpha_L\beta_2$.

Descripción del Arte Relacionado

Las integrinas de leucocitos y las moléculas de adhesión intercelular (ICAM por sus siglas en inglés) desempeñan papeles esenciales en la adhesión de leucocitos a células objetivo y matrices extracelulares. La subfamilia de las integrinas β_2 (CD18) tiene cuatro miembros, cada uno consistente en una cadena α relacionada pero distinta, emparejada de manera no covalente con CD18: la integrina $\alpha_L\beta_2$ (LFA-1, CD11a/CD18), la integrina $\alpha_M\beta_2$ (Mac-1, CD11b/CD18), la integrina $\alpha_X\beta_2$ (p150/95, CD11c/CD18) y la integrina $\alpha_D\beta_2$ (CD11d/CD18) (Bochner ed., *Moléculas de Adhesión en Enfermedad Alérgica*, Marcel Dekker Inc., pp. 1-24 (1997)). Entre ellas, se ha mostrado que LFA-1 es dominante para la adhesión celular y migración transendotelial de las células T, eosinófilos y otros leucocitos a los tejidos inflamados (Garmberg, *Curr. Opin. Cell Biology*, 9 643-650 (1997)); Panes et al., *Br. J. Pharmacology*, 126, 537-550 (1999)). LFA-1 se une a la familia ICAM (ICAM-1, -2, -3, 4-, 5-) de moléculas expresadas sobre múltiples tipos celulares tales como células endoteliales vasculares, células dendríticas, células epiteliales, macrófagos y linfoblastos T (Dustin et al., *J Immunology*, 137, 245-254 (1986)). Además,

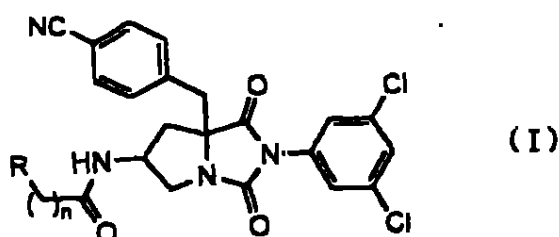
las interacciones LFA-1/ICAM-1 y LFA-1/ICAM-3 pueden actuar como señales coestimuladoras requeridas para la activación de células T (Wingren et al., *Crit. Rev. in Immunology*, 15, 235-253 (1995)).

La migración celular y la coactivación de células T son procesos importantes en varias condiciones de enfermedades inflamatorias. Un papel dominante de LFA-1 en la mediación de eventos inflamatorios es mostrado en diversos modelos animales diferentes de enfermedades inflamatorias en las cuales los anticuerpos a LFA-1 o ICAM-1 inhiben significativamente el desarrollo de puntos extremos terapéuticos (Rothlein et al., *Kidney International*, 41, 617 (1992); Iigo et al., *J. Immunology*, 147, 4167 (1991); Bennet et al., *J. Pharmacol. and Exp. Therapeutics*, 280, 988 (1997)). Además, un anticuerpo monoclonal humanizado a CD11a (la cadena alfa de LFA-1) ha mostrado eficacia en pacientes con psoriasis (Gottlieb et al., *J. Am. Acad. Dermatology*, 42, 428-35 (2000)).

Además, se ha mostrado que los anticuerpos contra LFA-1 suprimen el rechazo después del trasplante de órganos (Poston et al., *Transplantation* 69, 2005-2013 (2000); Nakakura et al., *Transplantation* 62, 547-552 (1996)). WO 94/04188 describe el uso de anticuerpos monoclonales dirigidos contra la integrina $\alpha\beta_2$ para todos los trasplantes.

SUMARIO DE LA INVENCIÓN

La presente invención se refiere a unos compuestos novedosos de fórmula (I):



en la cual R es un átomo de hidrógeno, un grupo hidroxilo o un grupo carbamoilo, y n es 1 o 2, o una sal farmacéuticamente aceptable de los mismos.

DESCRIPCIÓN DETALLADA DE LA INVENCION

Los compuestos deseados de la presente invención pueden existir en forma de isómeros ópticos basados en átomos asimétricos de los mismos, y la presente invención también incluye estos isómeros ópticos y mezclas de los mismos.

En una realización de la presente invención, la configuración estérica de un enlace no necesita ser fija. Los compuestos de la presente invención pueden ser un compuesto con una configuración única o una mezcla con diversas configuraciones diferentes.

En una realización preferida de los compuestos de fórmula (I), R es un átomo de hidrógeno.

En otra realización preferida de los compuestos de fórmula (I), R es un grupo hidroxilo.

En aún otra realización preferida de los compuestos de fórmula (I), R es un grupo carbamoilo.

En una realización más preferida de los compuestos de fórmula (I), n es 1.

En otra realización más preferida de los compuestos de fórmula (I), n es 2.

En una realización preferida adicional de los compuestos de fórmula (I), R es un átomo de hidrógeno y n es 1.

En otra realización preferida adicional de los compuestos de fórmula (I), R es un grupo hidroxilo y n es 1.

En aún otra realización preferida adicional de los compuestos de fórmula (I), R es un grupo carbamoilo y n es 2.

Los compuestos más preferidos de la presente invención son seleccionados de los siguientes compuestos:

(5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-acetilamino-1,3-diazabicyclo[3.3.0]octano-2,4-diona;

(5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-[(2-hidroxi-acetil)amino]-1,3-diazabicyclo[3.3.0]octano-2,4-diona;

(5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-[(3-carbamoil-propionil)amino]-1,3-diazabicyclo[3.3.0]octano-2,4-diona.

La característica de los presentes compuestos es la combinación del grupo acilamino en la posición 7 y el grupo 4-cianobencilo en la posición 5 del núcleo de 1,3-diazabicyclo[3.3.0]octano, en donde tal característica no es descrita específicamente en publicaciones previas.

Los compuestos de la presente invención tienen una potente actividad inhibidora contra la adhesión celular mediada por LFA-1 y la coactivación de células T mediada por LFA-1, y también muestran excelente biodisponibilidad después de la administración oral, lo cual refleja la mejoría general en (a) unión de proteína plasmática, (b) solubilidad acuosa y (c) lipofilicidad. Los compuestos de la presente invención, por lo tanto, muestran excelente eficacia in vivo contra las condiciones desfavorables causadas por la adhesión celular mediada por LFA-1.

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Además, los compuestos de la presente invención también tienen una potente actividad antagonista sobre el receptor de sustancia P, es decir, el receptor de neuroquinina (NK1). Se considera que los antagonistas de receptor de sustancia P son útiles para el tratamiento de enfermedades inflamatorias tales como asma, artritis reumatoide, enfermedad inflamatoria intestinal, cistitis y otros trastornos gástricos (Kranefeld et al., *Int. Immunopharmacology*, 1, 1629-1650 (2001); Swain et al., *Ann. Rep. Med. Chem.*, 34, 51-60 (1999); Ohnmacht Jr. et al., *Ann. Rep. Med. Chem.*, 33, 71-80 (1998)). Así, los compuestos de la presente invención tienen excelente potencial terapéutico contra las condiciones desfavorables causadas o mediadas por la sustancia P. También, los compuestos de la presente invención puede mostrar excelentes efectos sobre el tratamiento o prevención de enfermedades inflamatorias debidas a las actividades dobles de la inhibición de adhesión celular mediada por LFA-1 y el antagonismo de receptor de sustancia P.

Además, los compuestos de fórmula (I) tienen citotoxicidad reducida y baja actividad inhibidora de citocromo P450 en comparación con aquéllos descritos previamente y, por lo tanto, los compuestos de la presente invención pueden tener un potencial reducido de efectos secundarios.

Los compuestos de la presente invención pueden ser usados clínicamente en una forma libre o en forma de sales farmacéuticamente aceptables de los mismos. Las sales farmacéuticamente aceptables incluyen una sal de adición de ácido con un ácido inorgánico o un ácido orgánico, y una sal con una base inorgánica, una base orgánica o un aminoácido. Las sales farmacéuticamente aceptables también incluyen una sal

intramolecular de los mismos, o un solvato o hidrato de los mismos.

Los compuestos de la presente invención pueden ser formulados como una composición farmacéutica que comprende una cantidad terapéuticamente efectiva del compuesto tal se definió anteriormente y un portador o diluyente farmacéuticamente aceptable. El portador o diluyente farmacéuticamente aceptable puede ser, por ejemplo, ligadores (por ejemplo jarabe, goma arábica, gelatina, sorbitol, tragacanto, polivinilpirrolidona), excipientes (por ejemplo lactosa, sucrosa, almidón de maíz, fosfato de potasio, sorbitol, glicina), lubricantes (por ejemplo estearato de magnesio, talco, polietilenglicol, sílice), desintegradores (por ejemplo almidón de papa), agentes humectantes (por ejemplo laurilsulfato de sodio), y similares.

Los compuestos deseados de la presente invención o sales farmacéuticamente aceptables de los mismos pueden ser administrados ya sea oral o parenteralmente, y pueden ser usados como una preparación farmacéutica adecuada. Estas preparaciones farmacéuticas pueden tener la forma de una preparación sólida tal como una tableta, un gránulo, una cápsula y un polvo, o la forma de una preparación líquida tal como una solución, suspensión y emulsión, cuando son administradas oralmente. Cuando son administradas de manera parenteral, las preparaciones farmacéuticas pueden tener la forma de un supositorio, una preparación para inyección o una preparación para goteo intravenoso usando agua destilada para inyección, una solución de sal fisiológica, una solución de glucosa acuosa, y así sucesivamente, y una inhalación por un proceso convencional.

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La dosis de los compuestos deseados de la presente invención o sales farmacéuticamente aceptables de los mismos varía dependiendo del método de administración, edad, sexo, peso corporal y condición del paciente, pero, en general, la dosis diaria es preferiblemente aproximadamente 0,1 a 100 mg/kg/día, particularmente preferiblemente 1 a 100 mg/kg/día.

Los compuestos de la presente invención pueden ser usados para tratar o prevenir las condiciones mediadas por LFA-1 en un paciente, por ejemplo un paciente humano. Los compuestos de la presente invención pueden ser también usados para el tratamiento de un paciente que padece o es susceptible a condiciones mediadas por LFA-1. Unos ejemplos de condiciones mediadas por LFA-1 incluyen enfermedades inflamatorias, enfermedades autoinmunes y enfermedades alérgicas.

Los compuestos de la presente invención pueden ser también usados para el tratamiento o prevención de condiciones causadas o mediadas por la sustancia P en un paciente, así como para el tratamiento de un paciente que padece o es susceptible a tales condiciones. Unos ejemplos de las condiciones pueden ser las enfermedades inflamatorias.

Los compuestos de la presente invención pueden ser usados para el tratamiento o prevención de enfermedades tales como artritis reumatoide, asma, enfermedad pulmonar obstructiva crónica, condiciones alérgicas, síndrome del sufrimiento respiratorio del adulto, SIDA, enfermedades cardiovasculares, trombosis, agregación dañina de plaquetas, reoclusión después de una trombólisis, lesión de reperfusión, enfermedades inflamatorias cutáneas (por ejemplo psoriasis, eczema, dermatitis de contacto, dermatitis atópica), osteoporosis,

osteoartritis, aterosclerosis, arteriosclerosis incluyendo arteriosclerosis asociada con trasplante, enfermedades neoplásicas incluyendo metástasis de crecimientos neoplásicos o cancerosos, desprendimiento de retina, diabetes tipo I, esclerosis múltiple, lupus sistémico eritematoso, condiciones inflamatorias oftálmicas, enfermedades inflamatorias intestinales (enfermedad de Crohn y colitis ulcerosa), cistitis, trastornos gástricos, enteritis regional, Síndrome de Sjogren y otras enfermedades autoinmunes.

Los compuestos de la presente invención pueden ser también usados para el rechazo (es decir, rechazo crónico y rechazo agudo) después del trasplante de órganos, incluyendo rechazo de aloinjerto (enfermedad de huésped versus injerto) y enfermedad de injerto versus huésped.

Los compuestos de la presente invención pueden ser usados preferiblemente para el tratamiento o la prevención de psoriasis, artritis reumatoide, enfermedades inflamatorias intestinales (enfermedad de Crohn, colitis ulcerosa), lupus sistémico eritematoso, dermatitis atópica, síndrome de Sjogren, y rechazo después del trasplante de órganos (rechazo de aloinjerto y enfermedad de injerto versus huésped).

Los compuestos de la presente invención pueden ser adicionalmente usados preferiblemente para el tratamiento o la prevención de artritis reumatoide, asma, enfermedad pulmonar obstructiva crónica, psoriasis, esclerosis múltiple, y rechazo después del trasplante de órganos.

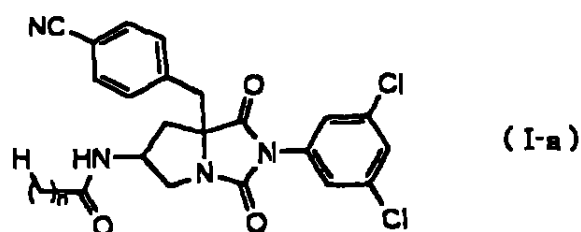
Los compuestos de la presente invención pueden ser también adicionalmente usados preferiblemente para el tratamiento o la prevención de enfermedades inflamatorias tales como asma,

enfermedad inflamatoria intestinal, cistitis y otros trastornos gástricos.

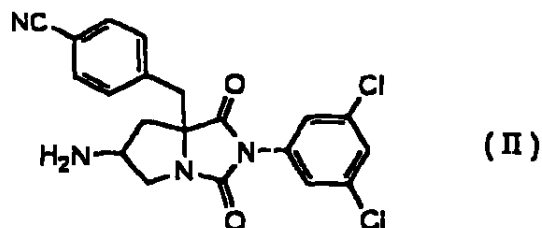
De acuerdo con la presente invención, los compuestos deseados (I) pueden ser preparados de acuerdo con uno de los siguientes métodos:

Método A:

Entre los compuestos de la presente invención, un compuesto de fórmula (I-a):



en la cual n es igual a como se definió anteriormente, o una sal farmacéuticamente aceptable del mismo, puede ser preparado condensando un compuesto de fórmula (II):



o una sal del mismo, con un compuesto de fórmula (III-a):



en la cual n es igual a como se definió anteriormente, una sal del mismo, o un derivado reactivo del mismo, seguido por la conversión del compuesto resultante en una sal farmacéuticamente aceptable del mismo, si se desea.

La sal de los compuestos (II) y (III-a) puede ser, por ejemplo, una sal con un ácido inorgánico u orgánico (por

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ejemplo trifluoroacetato, hidrocloruro, sulfato), o una sal con una base inorgánica (por ejemplo una sal de metal alcalino tal como una sal de sodio o una sal de potasio, una sal de metal alcalinotérreo tal como una sal de bario o una sal de calcio).

La reacción de condensación del compuesto (II) o una sal del mismo con el compuesto (III-a) o una sal del mismo puede ser llevada a cabo en presencia de un reactivo de condensación, con o sin una base en un solvente adecuado.

El reactivo de condensación puede ser seleccionado de reactivos de condensación convencionales que pueden ser usados para una síntesis de péptido, por ejemplo BOP-Cl, reactivo BOP, DCC, EDC o CDI. El reactivo de condensación puede ser preferiblemente usado con un activador (por ejemplo HOBT).

La base puede ser seleccionada de bases orgánicas convencionales tales como una alquilamina (por ejemplo DIEA, Et₃N), una amina cíclica (por ejemplo DBU, DBN, 4-metilmorfolina) y piridinas (por ejemplo piridina, DMAP), y bases inorgánicas convencionales tales como un carbonato de metal alcalino (por ejemplo Na₂CO₃, K₂CO₃), un carbonato de hidrógeno de metal alcalino (por ejemplo NaHCO₃, KHCO₃), un hidróxido de metal alcalino (por ejemplo NaOH, KOH) y similares.

El solvente puede ser seleccionado de uno cualquiera que no perturbe la reacción de condensación, por ejemplo ésteres (por ejemplo acetato de metilo, acetato de etilo), haloalcanos (por ejemplo CHCl₃, CH₂Cl₂), éteres (por ejemplo dietil éter, THF, DME, dioxano), amidas (por ejemplo DMF, N-metilpirrolidona), cetonas (por ejemplo acetona, metil etil cetona), CH₃CN, DMSO y H₂O, y una mezcla de estos solventes. La reacción puede ser

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llevada a cabo a una temperatura de -50°C a 50°C , preferiblemente desde 0°C hasta la temperatura ambiente.

La reacción de condensación del compuesto (II) o una sal del mismo con el derivado reactivo del compuesto (III-a) es llevada a cabo en presencia o ausencia de una base en un solvente adecuado o sin solvente.

Unos ejemplos del derivado reactivo del compuesto (III-a) son un haluro de ácido (por ejemplo un cloruro de ácido), un éster reactivo (por ejemplo un éster con p-nitrofenol), un anhídrido del mismo, un anhídrido mezclado con otro ácido carboxílico (por ejemplo un anhídrido mezclado con ácido isobutírico), y similares.

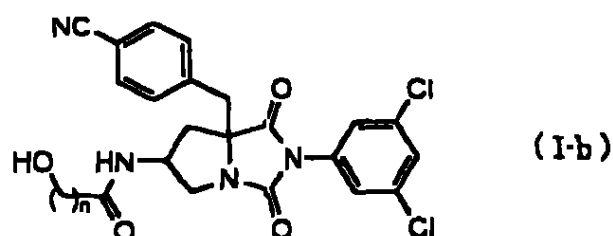
La base puede ser seleccionada de bases orgánicas convencionales tales como una alquilamina (por ejemplo DIEA, Et_3N), una amina cíclica (por ejemplo DBU, DBN, 4-metilmorfolina) y piridinas (por ejemplo piridina, DMAP), y bases inorgánicas convencionales tales como un carbonato de metal alcalino (por ejemplo Na_2CO_3 , K_2CO_3), un carbonato de hidrógeno de metal alcalino (por ejemplo NaHCO_3 , KHCO_3), un hidróxido de metal alcalino (por ejemplo NaOH , KOH) y similares.

El solvente puede ser seleccionado de uno cualquiera que no perturbe la reacción de condensación, por ejemplo ésteres (por ejemplo acetato de metilo, acetato de etilo), haloalcanos (por ejemplo CHCl_3 , CH_2Cl_2), éteres (por ejemplo dietil éter, THF, DME, dioxano), amidas (por ejemplo DMF, N-metilpirrolidona), cetonas (por ejemplo acetona, metil etil cetona), CH_3CN , DMSO y H_2O , y una mezcla de estos solventes.

La reacción de condensación puede ser llevada a cabo a una temperatura de -30°C hasta la temperatura ambiente.

Método B:

Entre los compuestos de la presente invención, un compuesto de fórmula (I-b):



en la cual n es igual a como se definió anteriormente, o una sal farmacéuticamente aceptable del mismo, puede ser preparado por condensación del compuesto (II) o una sal del mismo con un compuesto de fórmula (III-b):



en la cual R^1O es un grupo hidroxilo protegido o no protegido, y n es igual a como se definió anteriormente, una sal del mismo o un derivado reactivo del mismo, seguido por remoción del grupo de protección, y adicionalmente conversión del compuesto resultante en una sal farmacéuticamente aceptable del mismo, si es necesario.

La sal del compuesto (III-b) puede ser, por ejemplo, una sal con una base inorgánica (por ejemplo una sal de metal alcalino tal como una sal de sodio o una sal de potasio, y una sal de metal alcalinotérreo tal como una sal de bario y una sal de calcio).

El grupo de protección para el grupo hidroxilo puede ser seleccionado de grupos de protección convencionales para un grupo hidroxilo que pueden ser fácilmente removidos por un

método convencional. Unos ejemplos de tales grupos de protección incluyen un grupo trialkilsililo (por ejemplo, un grupo trimetilsililo, un grupo trietilsililo y un grupo t-butildimetilsililo), un grupo bencilo, un grupo metilo y un grupo tetrahidropiraniilo.

La reacción de condensación del compuesto (II) o una sal del mismo con el compuesto (III-b) en el cual R^1O es un grupo hidroxilo protegido, una sal del mismo o un derivado reactivo del mismo, puede ser llevada a cabo en un procedimiento similar al que se describió en el Método A.

La remoción del grupo de protección puede ser llevada a cabo por un método usual que es seleccionado de acuerdo con el grupo de protección a ser removido, por ejemplo hidrólisis, tratamiento con ácido, tratamiento con BBr_3 y reducción catalítica.

La hidrólisis puede ser llevada a cabo usando una base inorgánica tal como un hidróxido de metal alcalino (por ejemplo $LiOH$, $NaOH$ y KOH) en un solvente adecuado tal como éteres (por ejemplo dietil éter, dioxano y THF), alcoholes (por ejemplo $MeOH$, $EtOH$), CH_3CN , $DMSO$, H_2O y similares a temperatura ambiente o con calentamiento.

El tratamiento con ácido puede ser llevado a cabo usando un ácido inorgánico o un ácido orgánico tal como hidrocloruro, hidrobromuro, ácido acético, ácido p-toluenosulfónico y ácido trifluoroacético en un solvente adecuado tal como éteres (por ejemplo dietil éter, dioxano, THF), haloalcanos (por ejemplo $CHCl_3$, CH_2Cl_2), alcoholes (por ejemplo $MeOH$, $EtOH$), CH_3CN , $DMSO$, H_2O y similares a temperatura ambiente o con calentamiento.

La reducción catalítica puede ser llevada a cabo usando un catalizador tal como paladio sobre carbón activado y níquel Raney bajo una atmósfera de hidrógeno a temperatura ambiente o con calentamiento en un solvente adecuado tal como éteres (por ejemplo dietil éter, dioxano, THF), ésteres (por ejemplo acetato de metilo, acetato de etilo), alcoholes (por ejemplo MeOH, EtOH), CH_3CN , AcOH, H_2O y similares.

El tratamiento con BBr_3 para la desmetilación puede ser llevado a cabo en un solvente adecuado (por ejemplo THF, CH_2Cl_2 , AcOH) a una temperatura de -78°C hasta 50°C .

En caso de que el compuesto (III-b) en el cual R^1O es un grupo hidroxilo sea usado para la reacción de condensación, el grupo hidroxilo del compuesto (III-b) debe ser protegido in situ antes de la reacción de condensación.

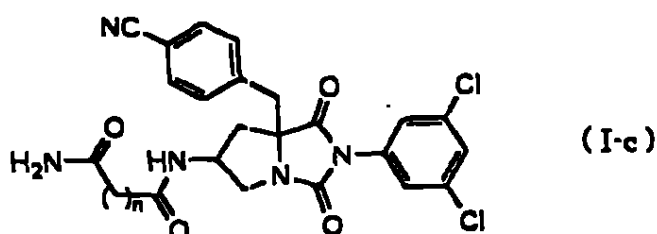
La protección del grupo hidroxilo puede ser llevada a cabo haciendo reaccionar el compuesto (III-b) con un haluro de trialquilsililo en un solvente adecuado en presencia de una base. Unos ejemplos del haluro de trialquilsililo incluyen cloruro de trimetilsililo, cloruro de trietilsililo y cloruro de t-butildimetilsililo. La base puede ser seleccionada de las bases convencionales que son usadas para la protección del grupo hidroxilo, por ejemplo trietilamina, imidazol y piridina. El solvente puede ser seleccionado de uno cualquiera que no perturbe la reacción de condensación, por ejemplo ésteres (por ejemplo acetato de metilo, acetato de etilo), hidrocarburos aromáticos (por ejemplo benceno, tolueno), haloalcanos (por ejemplo CHCl_3 , CH_2Cl_2), éteres (por ejemplo dietil éter, THF, DME, dioxano), amidas (por ejemplo DMF, N-metilpirrolidona), cetonas (por ejemplo acetona, metil etil cetona), CH_3CN , DMSO y

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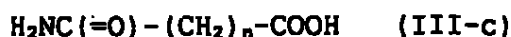
una mezcla de estos solventes. La reacción puede ser llevada a cabo a una temperatura de -50°C a 50°C , preferiblemente desde 0°C hasta la temperatura ambiente. El compuesto protegido puede ser aislado en un procedimiento usual, si es necesario.

Método C:

Entre los compuestos de la presente invención, un compuesto de fórmula (I-c):



en la cual n es igual a como se definió anteriormente, o una sal farmacéuticamente aceptable del mismo, puede ser preparado por condensación del compuesto (II) con un compuesto de fórmula (III-c):



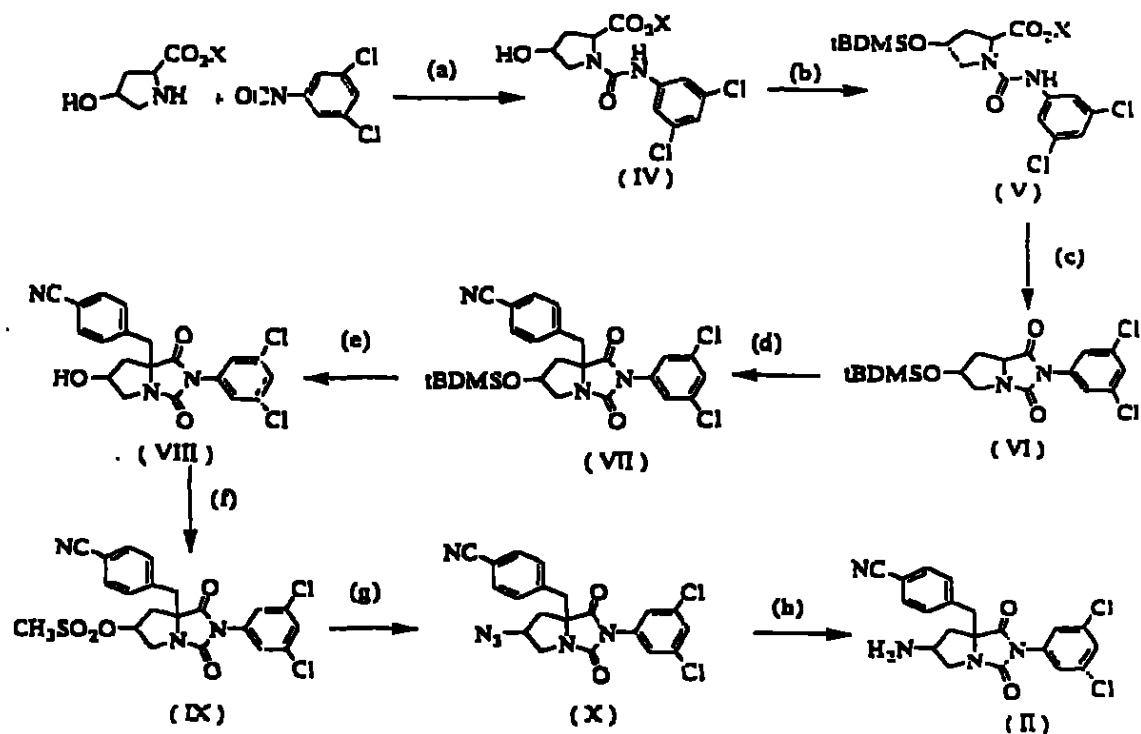
en la cual n es igual a como se definió anteriormente, una sal del mismo o un derivado reactivo del mismo, seguido por conversión del compuesto resultante en una sal farmacéuticamente aceptable del mismo, si se desea.

La sal de los compuestos (III-c) puede ser, por ejemplo, una sal con una base inorgánica (por ejemplo una sal de metal alcalino tal como una sal de sodio o una sal de potasio, una sal de metal alcalinotérreo tal como una sal de bario o una sal de calcio).

La reacción del compuesto (II) o una sal del mismo con el compuesto (III-c) o una sal del mismo puede ser llevada a cabo en un método similar al descrito en el Método A.

El compuesto de partida de fórmula (II) puede ser preparado de acuerdo con la descripción de WO 01/30781 o el siguiente esquema:

Esquema 1.



(En el esquema anterior, X es un grupo alquilo C_{1-6} o un grupo bencilo, y tBDMSO es un grupo t -butildimetilsililo.)

Paso (a): El compuesto (IV) puede ser preparado haciendo reaccionar un éster de alquilo C_{1-6} o bencilo de 4-hidroxiprolina con isocianato de 3,5-diclorofenilo en presencia de una base en un solvente adecuado.

La base puede ser seleccionada de bases orgánicas convencionales tales como una alquilamina (por ejemplo Et_3N , DIEA) y piridina, y bases inorgánicas convencionales tales como un hidrocarbonato de metal alcalino (por ejemplo NaHCO_3 , KHCO_3) y un carbonato de metal alcalino (por ejemplo Na_2CO_3 , K_2CO_3).

El solvente puede ser seleccionado de uno cualquiera que no perturbe la reacción de condensación, por ejemplo CH_2Cl_2 , DME, THF, DMF, HMPA o una mezcla de los mismos. La reacción puede ser llevada a cabo a una temperatura de -78°C a la temperatura ambiente.

Paso (b): El compuesto (V) puede ser preparado protegiendo el grupo hidroxilo del compuesto (IV). La protección puede ser llevada a cabo de una manera usual, por ejemplo haciendo reaccionar el compuesto (IV) con cloruro de ter-butildimetilsililo en presencia de imidazol en un solvente adecuado tal como CH_3CN . La reacción es llevada a cabo a una temperatura de 0°C hasta el punto de ebullición del solvente, preferiblemente a temperatura ambiente.

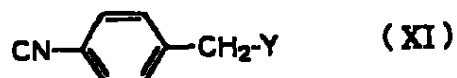
Paso (c): El compuesto (VI) puede ser preparado ciclizando el compuesto (V). La ciclización puede ser llevada a cabo en presencia o ausencia de una base en un solvente adecuado.

La base puede ser seleccionada de bases inorgánicas convencionales tales como un alcóxido de metal alcalino (por ejemplo NaOEt , NaOMe), un carbonato de metal alcalino (por ejemplo K_2CO_3 , Na_2CO_3) y un hidrocarbonato de metal alcalino (por ejemplo NaHCO_3), y bases orgánicas convencionales tales como piridina, DMAP, Et_3N y DIEA.

El solvente puede ser seleccionado de uno cualquiera que no perturbe la reacción de ciclización, por ejemplo tolueno, DME, CH_2Cl_2 , THF, CH_3CN , DMF, alcoholes (por ejemplo MeOH , EtOH) o una mezcla de los mismos. La reacción es llevada a cabo a una temperatura de 0°C hasta el punto de ebullición del solvente, preferiblemente a 50°C hasta 100°C .

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Paso (d): El compuesto (VII) puede ser preparado condensando el compuesto (VI) con un compuesto de fórmula (XI):



en la cual Y es un grupo de salida.

El grupo de salida puede ser seleccionado de un átomo de halógeno (por ejemplo un átomo de cloro, un átomo de bromo y un átomo de yodo), un grupo p-toluenosulfoniloxi y un grupo metanosulfoniloxi.

La reacción de condensación puede ser llevada a cabo en presencia de una base en un solvente adecuado.

La base puede ser seleccionada de bases convencionales tales como una amida de metal alcalino (por ejemplo LDA, KHMDS con o sin LiCl).

El solvente puede ser seleccionado de uno cualquiera que no perturbe la reacción de condensación, por ejemplo dietil éter, DME, THF, DMF, HMPA o una mezcla de los mismos. La reacción puede ser llevada a cabo a una temperatura de -78°C a la temperatura ambiente.

Paso (e): El compuesto (VIII) puede ser preparado por desprotección del compuesto (VII). La desprotección puede ser llevada a cabo por un método usual, por ejemplo tratando el compuesto con HF/piridina, n-Bu₄NF o un ácido (por ejemplo HCl, AcOH, TFA, p-TsOH) en un solvente adecuado o sin solvente.

El solvente puede ser seleccionado de uno cualquiera que no perturbe la reacción de condensación, por ejemplo CH₃CN, THF, DMF, alcoholes (por ejemplo MeOH, EtOH) o una mezcla de los

mismos. La reacción puede ser llevada a cabo a una temperatura de -78°C a la temperatura ambiente.

Paso (f): El compuesto (IX) puede ser preparado haciendo reaccionar el compuesto (VIII) con cloruro de metanosulfonilo en presencia de una base en un solvente adecuado.

La base puede ser seleccionada de bases convencionales tales como Et_3N , DIEA, piridina, NaHCO_3 , KHCO_3 , Na_2CO_3 , K_2CO_3 .

El solvente puede ser seleccionado de uno cualquiera que no perturbe la reacción, por ejemplo CH_2Cl_2 , THF, DMF, HMPA, CH_3CN , tolueno. La reacción puede ser llevada a cabo a una temperatura de -20°C a 50°C .

Paso (g): El compuesto (X) puede ser preparado haciendo reaccionar el compuesto (IX) con un azuro de metal alcalino (por ejemplo NaN_3).

La reacción de sustitución puede ser llevada a cabo a una temperatura de 0°C hasta 100°C en un solvente orgánico.

El solvente puede ser seleccionado de uno cualquiera que no perturbe la reacción, por ejemplo CH_2Cl_2 , THF, DMF, CH_3CN y tolueno.

Paso (h): El compuesto (II) puede ser preparado reduciendo el compuesto (X). La reducción puede ser llevada a cabo bajo condiciones de hidrogenación catalítica, por ejemplo en presencia de un catalizador de Pd o Pt (por ejemplo, Pd-C, PtO_2) en un solvente adecuado bajo una atmósfera de H_2 a temperatura ambiente.

El solvente puede ser seleccionado de uno cualquiera que no perturbe la reacción, por ejemplo EtOAc, MeOH y EtOH.

En la presente descripción y las reivindicaciones, el grupo alquilo C_{1-6} significa un grupo alquilo de cadena lineal o

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cadena ramificada que tiene 1 a 6 átomos de carbono, por ejemplo un grupo metilo, etilo, propilo, isopropilo, butilo, isobutilo, etc., preferiblemente uno que tiene 1 a 4 átomos de carbono.

Abreviaturas

AcOEt: Acetato de etilo (=EtOAc)

AcOH: Ácido acético

BOP-Cl: Cloruro bis(2-oxo-3-oxazolidinil)fosfínico

Reactivo BOP: Hexafluorofosfato de benzotriazol-1-iloxi-
tris(dimetilamino)fosfonio

BSA: Albúmina de suero bovino

CDI: Carbonildiimidazol

DBN: 1,5-diazabicyclo[4.3.0]non-5-eno

DBU: 1,8-diazabicyclo[5.4.0]undec-7-eno

DCC: 1,3-diciclohexilcarbodiimida

DIEA: Diisopropiletilamina

DMAP: 4-dimetilaminopiridina

DME: Dimetoxietano

DMF: Dimetilformamida

DMSO: Dimetilsulfóxido

EDC: Hidrocloruro de 1-(3-dimetilaminopropil)-3-
etilcarbodiimida

Et: Etilo

EtOH: Etanol

HBSS: Solución de sal balanceada de Hank

HMPA: Hexametilfosforamida

HOBT: Hidrato de 1-hidroxibenzotriazol

HSA: Albúmina de suero humano

KHMDS: Hexametildisilazuro de potasio (=bis(trimetilsilil)amida de potasio)

LDA: Diisopropilamida de litio

Me: Metilo

MeOH: Metanol

n-Bu: n-butilo

tBDMS: ter-butildimetilsililo

THF: Tetrahidrofurano

TFA: Ácido trifluoroacético

p-TsOH: Ácido p-toluenosulfónico

Ejemplos

Los compuestos de la presente invención son ejemplificados por los siguientes ejemplos pero no limitados por los mismos.

Ejemplo 1. (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-acetilamino-1,3-diazabicyclo[3.3.0]octano-2,4-diona

A una solución de (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-amino-1,3-diazabicyclo[3.3.0]octano-2,4-diona (78,5 mg) en THF (5 ml) se añadió anhídrido acético (1,0 ml). La mezcla de reacción fue agitada por 2 horas a 45°C, y la mezcla fue concentrada y purificada por cromatografía preparativa de capa delgada (gel de sílice; CH₂Cl₂) para dar el compuesto del título (84 mg). MS (m/z) 478,8 (MNa⁺).

Ejemplo 2. (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-[(3-carbamoyl-propionil)amino]-1,3-diazabicyclo[3.3.0]octano-2,4-diona

Una mezcla de (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-amino-1,3-diazabicyclo[3.3.0]octano-2,4-diona (82,7 mg), ácido succínico (45,86 mg), EDC (93,12 mg), HOBT (61,24 mg) y DIEA (104,79 µl) en THF (5 ml) fue agitada toda la noche

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a temperatura ambiente. La mezcla de reacción fue concentrada y purificada por cromatografía líquida de alto rendimiento (HPLC) (columna Beckman 5 μ C18; eluido con un gradiente de H₂O/MeCN (10-100%)/0,1% TFA) para dar 72 mg del compuesto del título. MS (m/z) 536 (MNa⁺).

Ejemplo 3. (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-[(2-carbamoilacetil)amino]-1,3-diazabicyclo[3.3.0]octano-2,4-diona

Una mezcla de (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-amino-1,3-diazabicyclo[3.3.0]octano-2,4-diona (200 mg), ácido malonámico (59,5 mg), EDC (112 mg), HOBT (97,5 mg) y DIEA (168 μ l) en THF (5 ml) fue agitada toda la noche a temperatura ambiente. La mezcla de reacción fue evaporada. El residuo fue disuelto en EtOAc y la solución resultante fue lavada con agua, solución de NaHCO₃ acuosa saturada, solución salina, secada (Na₂SO₄) y concentrada para dar 212 mg del compuesto del título. MS (m/z) 500 (MH⁺).

Ejemplo 4. (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-[(3-hidroxipropionil)amino]-1,3-diazabicyclo[3.3.0]octano-2,4-diona

Paso 1: Una mezcla de (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-amino-1,3-diazabicyclo[3.3.0]octano-2,4-diona (0,300 g), ácido 3-metoxipropiónico (0,209 μ l), EDC (0,224 g), HOBT (0,221 g) y DIEA (0,38 μ l) en THF (15 ml) fue agitada toda la noche a temperatura ambiente. La mezcla de reacción fue evaporada. El residuo fue purificado por HPLC (columna Beckman 5 μ C18; eluido con un gradiente de H₂O/MeCN (10-100%)/0,1% AcOH) para dar una espuma. Ésta fue disuelta en EtOAc y la solución resultante fue lavada con agua, solución de NaHCO₃

acuosa saturada, solución salina, secada (Na_2SO_4) y concentrada para dar 0,259 g de (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-[(3-metoxipropionil)amino]-1,3-diazabicyclo[3.3.0]octano-2,4-diona. MS (m/z) 501 (MH^+).

Paso 2: BBr_3 (3 ml, 1M en CH_2Cl_2) fue añadido a una solución de (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-[(3-metoxipropionil)amino]-1,3-diazabicyclo[3.3.0]octano-2,4-diona (0,16 g) en CH_2Cl_2 (15 ml) a -78°C y la mezcla fue agitada por 8 horas a -78°C . La mezcla fue evaporada y el residuo fue purificado por HPLC (columna Beckman 5 μ C18; eluido con un gradiente de $\text{H}_2\text{O}/\text{MeCN}$ (10-100%)/0,1% AcOH) para dar una espuma. Ésta fue disuelta en EtOAc y la solución resultante fue lavada con agua, solución de NaHCO_3 acuosa saturada, solución salina, secada (Na_2SO_4) y concentrada para dar 0,119 g del compuesto del título. MS (m/z) 487 (MH^+).

Ejemplo 5. (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-[(2-hidroxiacetil)amino]-1,3-diazabicyclo[3.3.0]octano-2,4-diona

Paso 1: A una solución de (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-amino-1,3-diazabicyclo[3.3.0]octano-2,4-diona (150 mg) y DIEA (189 μl) en THF (4 ml) se añadió una solución de cloruro de benciloxiacetilo (57 μl) en THF (2 ml) y la mezcla fue agitada toda la noche a temperatura ambiente. La mezcla de reacción fue concentrada y el residuo fue captado en EtOAc. La solución resultante fue lavada con solución salina, secada (Na_2SO_4), filtrada y concentrada. El residuo fue purificado por HPLC (columna Beckman 5 μ C18; eluido con un gradiente de $\text{H}_2\text{O}/\text{MeCN}$ (10-100%)/0,1% AcOH) para dar una espuma. Ésta fue disuelta en EtOAc y la solución resultante fue lavada

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con agua, solución de NaHCO_3 acuosa saturada, solución salina, secada (Na_2SO_4) y concentrada para dar 0,135 g de (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-[(2-benciloxiacetil)amino]-1,3-diazabicyclo[3.3.0]octano-2,4-diona. MS (m/z) 563,4 [MH^+].

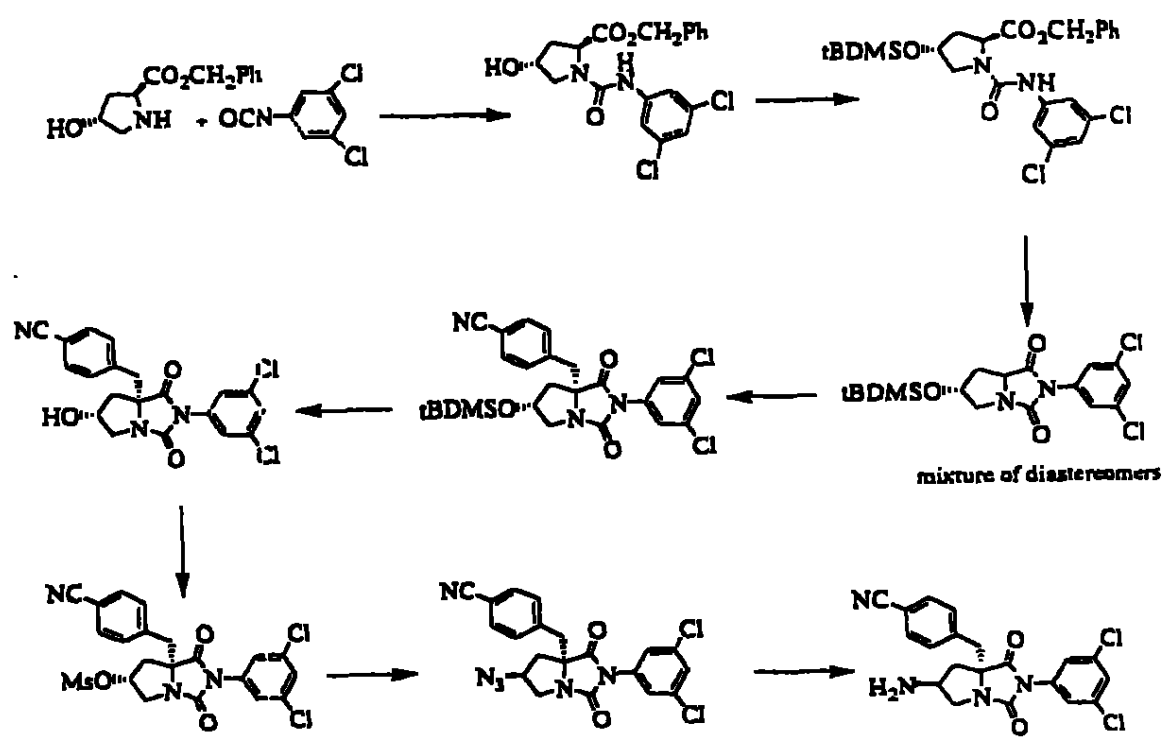
Paso 2: Se burbujeó hidrógeno a través de una solución de (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-[(2-benciloxiacetil)amino]-1,3-diazabicyclo[3.3.0]octano-2,4-diona del paso 1 (0,125 g) en EtOH (10 ml) que contenía Pd/C (5%, 15 mg) y la mezcla de reacción fue agitada toda la noche bajo una atmósfera de H_2 . La mezcla fue recargada con 5% Pd/C adicional (10 mg) y agitada toda la noche bajo una atmósfera de H_2 . La mezcla de reacción fue filtrada a través de un lecho de Celite y el filtrado fue concentrado. El residuo fue purificado por HPLC (columna Beckman 5 μ C18; eluido con un gradiente de $\text{H}_2\text{O}/\text{MeCN}$ (10-100%)/0,1% TFA) para dar 0,023 g del compuesto del título. MS /m/z) 473 [MH^+] y 495 [MNa^+].

Ejemplo de Referencia 1: (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-amino-1,3-diazabicyclo[3.3.0]octano-2,4-diona

El compuesto del título fue preparado de acuerdo con el siguiente esquema:

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Esquema 2.



(En el esquema anterior, tBDMSO es un grupo t-butildimetilsililoxi y MsO es un grupo metanosulfoniloxi.)

Paso 1: Se añadió ácido p-tolueno sulfónico (50,6 g) a una suspensión de L-4-trans-hidroxiprolina (25,25 g) en una mezcla de alcohol bencílico (100 ml) y benceno (250 ml) y la mezcla fue calentada bajo una trampa Dean Stark por 24 horas. La mezcla de reacción fue concentrada y se añadió dietil éter para precipitar el sólido. El sólido fue filtrado, lavado con dietil éter adicional y secado para producir 75 g de éster de bencilo de L-4-trans-hidroxiprolina.

Paso 2: A una suspensión de la sal de ácido sulfónico del éster de bencilo de L-4-trans-hidroxiprolina del paso 1 (40,43 g) en THF (500 ml) y DIEA (51,3 ml) se añadió isocianato de 3,5-diclorofenilo (22,1 g). Después de agitar toda la noche, la mezcla de reacción fue concentrada. El residuo fue disuelto en

EtOAc, lavado con HCl 0,5N, solución de NaHCO₃ acuosa saturada, solución salina, secado (Na₂SO₄), filtrado y concentrado. El residuo fue triturado en EtOAc/hexano (1:1) y el sólido blanco fue filtrado y purificado por cromatografía de columna instantánea (gel de sílice; hexano/EtOAc 2:1) para producir el éster de bencilo de (2S,4R)-2-[(3,5-diclorofenil)carbamoil]-4-hidroxiprolina (33,07 g).

Paso 3: A una suspensión del éster de bencilo de (2S,4R)-2-[(3,5-diclorofenil)carbamoil]-4-hidroxiprolina (33,07 g) en CH₃CN (800 ml) se añadió imidazol (11 g) y cloruro de ter-butildimetilsililo (13,64 g). Después de agitar por 48 horas, la mezcla de reacción fue concentrada. El residuo fue disuelto en EtOAc, lavado con HCl 0,5N, solución de NaHCO₃ acuosa saturada, solución salina, secado (Na₂SO₄), filtrado y concentrado. El residuo fue purificado por cromatografía de columna instantánea (gel de sílice; hexano/EtOAc 2:1) para dar el éster de bencilo de (2S,4R)-2-[(3,5-diclorofenil)carbamoil]-4-(ter-butildimetilsililo)prolina (44,45 g).

Paso 4: A una solución del éster de bencilo de (2S,4R)-2-[(3,5-diclorofenil)carbamoil]-4-(ter-butildimetilsililo)prolina (23,49 g) en CH₃CN (500 ml) se añadió DIEA (34,44 ml) y la mezcla fue calentada a reflujo. Después de permanecer en reflujo por 24 horas, la mezcla de reacción fue concentrada y purificada por cromatografía de columna instantánea (gel de sílice; hexano/EtOAc 1:1) para separar los dos diastereómeros de 3-(3,5-diclorofenil)-7-(ter-butildimetilsililo)-1,3-diazabicyclo[3.3.0]octano-2,4-diona.

Paso 5: El compuesto del paso 4, diastereómero A o B, (12,73 g) fue bencilado como sigue. Se añadió n-butil litio (30 ml, 1,6M en hexano) con agitación a una solución de diisopropilamina (6,5 ml) en THF (100 ML) a -78°C bajo una atmósfera de N_2 . La mezcla fue mantenida a esa temperatura por 30 minutos adicionales. La mezcla fue añadida por cánula a una solución de 3-(3,5-diclorofenil)-7-(ter-butildimetilsililoxi) -1, 3-diaza-biciclo [3.3.0] octano-2,4-diona (12,73 g) en THF seco (100 ml) a -78°C bajo una atmósfera de N_2 . Después de agitar a -78°C por 30 minutos, se añadió 4- ciano- α -bromotolueno (9,08 g) en THF (100 ml). La mezcla de reacción fue agitada a -78°C por 2,5 horas, entonces calentada lentamente hasta la temperatura ambiente y se dejó que permaneciera a temperatura ambiente por 0,5 hora. La mezcla de reacción fue concentrada y el residuo fue disuelto en EtOAc. La solución de EtOAc fue lavada con HCL 0,5N, solución de NaHCO_3 acuosa saturada, solución salina, secada (Na_2SO_4), filtrada y concentrada. El residuo fue purificado por cromatografía de columna instantánea (gel de sílice; hexano/EtOAc 24: 1 a 3:1) para dar (5S,7R) y (5R,7R) -5-(4-cianobencil)-3-(3,5-diclorofenil)-7-(terbutildimetil-sililoxi) -1, 3-diazabicyclo[3.3.0] octano-2,4-diona. Isómero (5S, 7R) : 7,6 g, MS : m/z 530 (M^+) ; y Isómero (5R, 7R) : 1,8 g, MS : m/z 530 (M^+) .

Paso 6: A una solución de (5S, 7R) -5- (4-cianobencil) -3-(3,5-diclorofenil) -7- (ter-butildimetilsililoxi) -1, 3-diazabicyclo-[3.3.0]octano-2,4-diona (1,0 g) en THF (1 ml) se añadió 70% HF/piridina (25 ml).

La mezcla de reacción fue agitada por 24 horas y después evaporada. El residuo fue disuelto en EtOAc y la solución resultante fue lavada con agua, solución NaHCO_3

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acuosa saturada, solución salina, secada (Na_2SO_4) y concentrada. El residuo fue purificado por cromatografía de columna instantánea (gel de sílice; $\text{MeOH}/\text{CH}_2\text{Cl}_2$ 2-7%) para dar (5S,7R)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-hidroxi-1,3-diazabicyclo[3.3.0]octano-2,4-diona (0.52 g). MS (m/z) 416 [MH^+].

Paso 7: A una solución de (5S,7R)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-hidroxi-1,3-diazabicyclo[3.3.0]octano-2,4-diona del paso 6 (0.52 g) en CH_2Cl_2 (8 ml) a 0°C se añadió DIEA (0,45 ml) seguida por cloruro de metanosulfonilo (0,15 ml) y la mezcla fue agitada por 1,5 horas. La mezcla de reacción fue diluida con CH_2Cl_2 y la mezcla resultante fue lavada con solución de NaHCO_3 acuosa saturada seguida por solución salina, secada (Na_2SO_4), filtrada y concentrada para dar 0,76 g de (5S,7R)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-metanosulfonilo-1,3-diazabicyclo[3.3.0]octano-2,4-diona. Este compuesto fue usado tal cual para el siguiente paso. MS (m/z) 501 [MH^+].

Paso 8: Se añadió NaN_3 a una solución de (5S,7R)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-metanosulfonilo-1,3-diazabicyclo[3.3.0]octano-2,4-diona del paso 7 (0,76 g) en DMF (5 ml) y la mezcla fue agitada por 24 horas. La mezcla de reacción fue dividida entre EtOAc y agua. La solución orgánica fue lavada con solución salina, secada (Na_2SO_4), filtrada y concentrada. El residuo fue purificado por cromatografía de columna instantánea (gel de sílice; CH_2Cl_2) para dar 0,46 g de (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-azuro-1,3-diazabicyclo[3.3.0]octano-2,4-diona. MS (m/z) 441 [MH^+].

diazabicyclo[3.3.0]octano-2,4-diona del paso 8 (0,42 g) en EtOH (15 ml) que contenía Pd/C (5%, 15 mg) y la mezcla de reacción fue agitada toda la noche bajo una atmósfera de H₂. La mezcla de reacción fue filtrada a través de un lecho de Celite y el filtrado fue concentrado. El residuo fue purificado por HPLC (columna Beckman 5 µ C18; eluido con un gradiente de H₂O/MeCN (10-100%)/0,1% TFA) para dar 0,21 g de (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-amino-1,3-diazabicyclo[3.3.0]octano-2,4-diona. MS (m/z) 415 [MH⁺].

Ejemplo de Referencia 2: (5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-amino-1,3-diazabicyclo[3.3.0]octano-2,4-diona

Paso 1: 3-(3,5-diclorofenil)-7-(ter-butildimetilsililoxi)-1,3-diazabicyclo[3.3.0]octano-2,4-diona fue preparada siguiendo procedimientos similares a los descritos en el Ejemplo de Referencia 1, pasos 1 a 4, pero reemplazando la sal de ácido p-tolueno sulfónico del éster de bencilo de L-4-trans-hidroxiprolina con hidrocloruro del éster de metilo de L-4-trans-hidroxiprolina.

Paso 2: La 3-(3,5-diclorofenil)-7-(ter-butildimetilsililoxi)-1,3-diazabicyclo[3.3.0]octano-2,4-diona del paso 1 fue tratada en procedimientos similares a los descritos en el Ejemplo de Referencia 1, pasos 5 a 9, para dar el compuesto del título.

Protocolo de Adhesión Celular

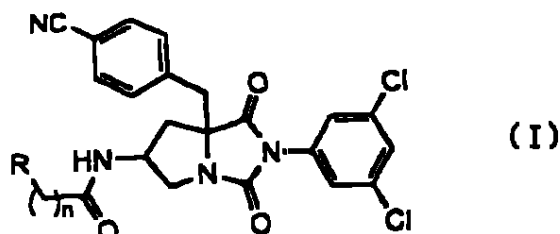
Adhesión Celular La proteína recombinante ICAM-1·Fc fue construida a partir de los 5 dominios extracelulares de ICAM-1 humana y fusión con la región constante de IgG humana. ICAM-1·Fc fue purificada por cromatografía de afinidad de Proteína A

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transferencia de 100 µl/receptáculo a placas Falcon Probind III e incubación toda la noche a 4°C. Los receptáculos recubiertos con BSA sirvieron como una medida de adhesión de medio no específico. Las placas lavadas fueron bloqueadas con una solución de 0,25% ovalbúmina en PBS por 1 hora a 37°C. Unas células Jurkat lavadas con HBSS fueron suspendidas hasta una concentración final de $2,5 \times 10^6/m$ en solución amortiguadora de adhesión TBSg (24 mM Tris pH 7,4, 0,14 M NaCl, 2,7 mM KCl, 2 mM glucosa, 0,1% HSA). Un volumen de 100 µl de células fue añadido a las placas recubiertas con ICAM-1-Fc bloqueadas y lavadas que contenían 100 µl de solución amortiguadora de placa (TBSg, 10 mM MgCl₂, 2% DMSO). La adhesión fue por 1 hora a 37°C. Las células no adherentes fueron removidas usando el lavador de placa EL404 (BioTek Instruments; Highland Park, VT). El número de células adherentes fue cuantificado midiendo la actividad enzimática de N-acetil-hexosaminidasa endógena usando el sustrato de enzima p-nitrofenol-N-acetil-β-D-glucosaminuro, pNAG. La cantidad de p-nitrofenol liberada fue medida leyendo la densidad óptica a 405 nm usando un espectrofotómetro de trayectoria vertical para cuantificar la unión celular (Lectora Cinética de Microplacas VMAX, Molecular Devices, Menlo Park, CA). Para estudios de competencia los compuestos de soluciones madre de 100% DMSO fueron diluidos en solución amortiguadora de placa al doble de la concentración de prueba requerida antes de la transferencia a la placa recubierta con ICAM-1-Fc y dilución en serie.

REIVINDICACIONES

1. Un compuesto de fórmula (I):



en la cual R es un átomo de hidrógeno, un grupo hidroxilo o un grupo carbamoilo, y n es 1 o 2, o una sal farmacéuticamente aceptable del mismo.

2. El compuesto o sal de acuerdo con la reivindicación 1, en el cual R es un átomo de hidrógeno.

3. El compuesto o sal de acuerdo con la reivindicación 1, en el cual R es un grupo hidroxilo.

4. El compuesto o sal de acuerdo con la reivindicación 1, en el cual R es un grupo carbamoilo.

5. El compuesto o sal de acuerdo con una cualquiera de las reivindicaciones 1-4, en el cual n es 1.

6. El compuesto o sal de acuerdo con una cualquiera de las reivindicaciones 1-4, en el cual n es 2.

7. El compuesto o sal de acuerdo con la reivindicación 1, en el cual R es un átomo de hidrógeno y n es 1.

8. El compuesto o sal de acuerdo con la reivindicación 1, en el cual R es un grupo hidroxilo y n es 1.

9. El compuesto o sal de acuerdo con la reivindicación 1, en el cual R es un grupo carbamoilo y n es 2.

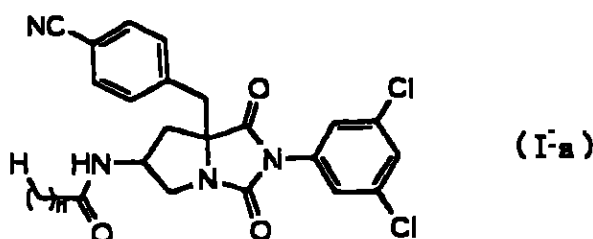
10. El compuesto o sal de acuerdo con la reivindicación 1,

(5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-acetilamino-1,3-diazabicciclo[3.3.0]octano-2,4-diona;

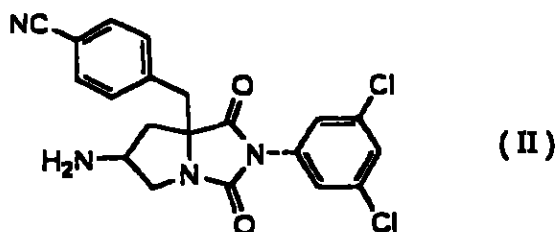
(5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-[(2-hidroxi-acetil)amino]-1,3-diazabicciclo[3.3.0]octano-2,4-diona;

(5S,7S)-5-(4-cianobencil)-3-(3,5-diclorofenil)-7-[(3-carbamoil-propionil)amino]-1,3-diazabicciclo[3.3.0]octano-2,4-diona.

11. Un proceso para preparar un compuesto de fórmula (I-a):



en la cual n es 1 o 2, o una sal farmacéuticamente aceptable del mismo, que comprende condensar un compuesto de fórmula (II):

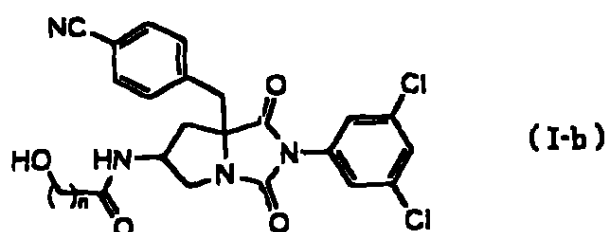


o una sal del mismo, con un compuesto de fórmula (III-a):

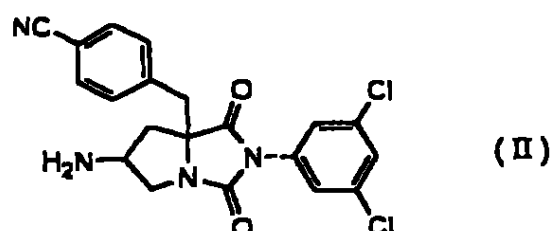


en la cual n es igual a como se definió anteriormente, una sal del mismo o un derivado reactivo del mismo, seguido por la conversión del compuesto resultante en una sal farmacéuticamente aceptable del mismo, si se desea.

12. Un proceso para preparar un compuesto de fórmula (I-b):



en la cual n es 1 o 2, o una sal farmacéuticamente aceptable del mismo, que comprende condensar un compuesto de fórmula (II):

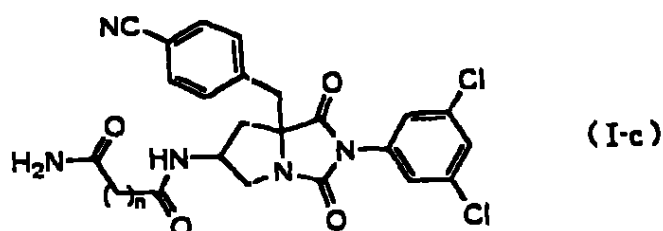


o una sal del mismo, con un compuesto de fórmula (III-b):



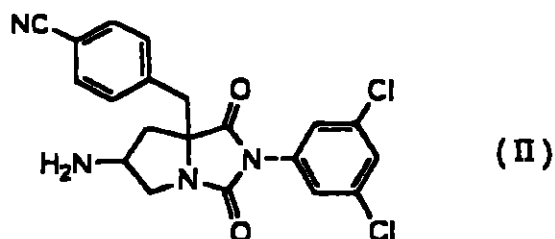
en la cual R^1O es un grupo hidroxilo protegido o no protegido, y n es igual a como se definió anteriormente, una sal del mismo o un derivado reactivo del mismo, seguido por remoción del grupo de protección, y adicionalmente conversión del compuesto resultante en una sal farmacéuticamente aceptable del mismo, si es necesario.

13. Un proceso para preparar un compuesto de fórmula (I-c):

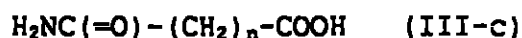


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en la cual n es 1 o 2, o una sal farmacéuticamente aceptable del mismo, que comprende condensar un compuesto de fórmula (II):



o una sal del mismo, con un compuesto de fórmula (III-c):



en la cual n es igual a como se definió anteriormente, una sal del mismo o un derivado reactivo del mismo, seguido por conversión del compuesto resultante en una sal farmacéuticamente aceptable del mismo, si se desea.

14. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva del compuesto o sal tal se expuso en una cualquiera de las reivindicaciones 1-10 en mezcla con un portador o diluyente farmacéuticamente aceptable.

15. Un método para el tratamiento o la prevención de una condición mediada por LFA-1 en un paciente, que comprende administrar una cantidad terapéuticamente efectiva del compuesto o sal tal como se expuso en una cualquiera de las reivindicaciones 1-10.

16. El método de acuerdo con la reivindicación 15, en el cual la condición es seleccionada de una enfermedad inflamatoria, una enfermedad autoinmune y una enfermedad alérgica.

que comprende administrar una cantidad terapéuticamente efectiva del compuesto o sal tal como se expuso en una cualquiera de las reivindicaciones 1-10.

18. El método de acuerdo con la reivindicación 17, en el cual la condición es una enfermedad inflamatoria.

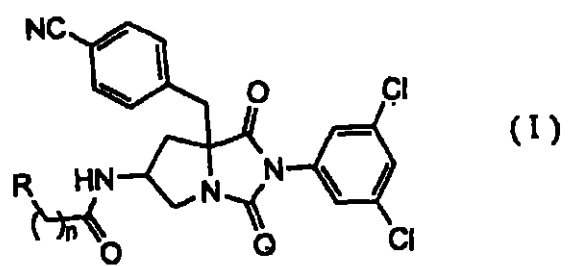
19. Un método para el tratamiento o prevención de una condición en un paciente, que comprende administrar una cantidad terapéuticamente efectiva del compuesto o sal tal como se expuso en una cualquiera de las reivindicaciones 1-10, en donde dicha condición es seleccionada de artritis reumatoide, asma, enfermedad pulmonar obstructiva crónica, condiciones alérgicas, síndrome del sufrimiento respiratorio del adulto, SIDA, enfermedades cardiovasculares, trombosis, agregación dañina de plaquetas, reoclusión después de una trombólisis, lesión de reperfusión, enfermedades inflamatorias cutáneas, osteoporosis, osteoartritis, aterosclerosis, arteriosclerosis, enfermedades neoplásicas, heridas, desprendimiento de retina, diabetes tipo I, esclerosis múltiple, lupus sistémico eritematoso, condiciones inflamatorias oftálmicas, enfermedades inflamatorias intestinales, cistitis, trastornos gástricos, enteritis regional, Síndrome de Sjogren y rechazo después del trasplante de órganos.

20. El método de acuerdo con la reivindicación 19, en el cual dicha condición es seleccionada de psoriasis, artritis reumatoide, enfermedades inflamatorias intestinales, lupus sistémico eritematoso, dermatitis atópica, síndrome de Sjogren, y rechazo después del trasplante de órganos.

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asma, enfermedad pulmonar obstructiva crónica, psoriasis, esclerosis múltiple, y rechazo después del trasplante de órganos.

22. El método de acuerdo con la reivindicación 19, en el cual dicha condición es seleccionada de asma, enfermedad inflamatoria intestinal, cistitis y trastorno gástrico.



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Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

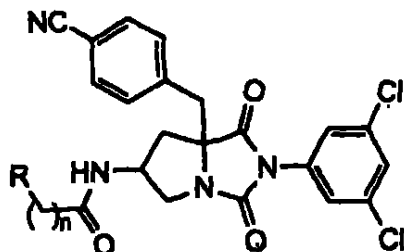
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For two-letter codes and other abbreviations, refer to the "Guid-
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ning of each regular issue of the PCT Gazette.

WO 03/066636 A1

(54) Title: INHIBITORS OF ALPHA L BETA 2 INTEGRIN MEDIATED CELL ADHESION



(I)

(57) Abstract: The present invention relates to a compound
of formula (I); wherein R is hydrogen atom, hydroxyl group
or carbamoyl group, and n is 1 or 2, or a pharmaceutically
acceptable salt thereof.

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PCT REQUEST

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0	For receiving Office use only	
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0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/ROH01 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2003)
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)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	0485-0225FPC
I	Title of Invention	INHIBITORS OF ALPHA L BETA 2 INTEGRIN MEDIATED CELL ADHESION
II	Applicant	
II-1	This person is:	applicant only
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II-9	Facsimile No.	011-81-6-6300-2695
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III-1-7	State of residence	US

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III-2	Applicant and/or Inventor	
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III-2-7	State of residence	US
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III-5-1	This person is:	applicant and inventor
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III-6-7	State of residence	JP

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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)	MURPHY, Jr., Gerald, M.
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IV-1-3	Telephone No.	(703) 205-8000
IV-1-4	Facsimile No.	(703) 205-8050
IV-1-5	e-mail	mailroom@bskb.com
IV-1-5	Agent's registration No.	28,977
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

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V-5	Precautionary Designation Statement In addition to the designations made under Items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under Item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	Exclusion(s) from precautionary designations	NONE	
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	07 February 2002 (07.02.2002)	
VI-1-2	Number	60/354,309	
VI-1-3	Country	US	
VI-2	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	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
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)	1	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

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VIII-4-1	Declaration: Inventorship (only for the purposes of the designation of the United States of America) Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought. This declaration is directed to the international application of which it forms a part (if filing declaration with application). I hereby declare that my residence, mailing address, and citizenship are as stated next to my name. I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.
II-4-1	Prior applications:	

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PCT REQUEST

6/9

0485-0225FPC

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		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
VIII-4-1 -1-1 VIII-4-1 -1-2 VIII-4-1 -1-3 VIII-4-1 -1-4 VIII-4-1 -1-5 VIII-4-1 -1-6	Name: Residence: (city and either US State, if applicable, or country) Mailing address: Citizenship: Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 28ter after the filing of the international application. The signature must be that of the inventor, not that of the agent) Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 28ter after the filing of the international application)	SIRCAR, Ila San Diego, California 4832 Riding Ridge Road US <i>Ila Sircar</i> 1/20/03

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PCT REQUEST

0485-0225FPC

Original (for SUBMISSION) - printed on 15.01.2003 11:16:16 AM

VIII-4-1 -2-1	Name:	MORNINGSTAR, Marshall
VIII-4-1 -2-2	Residence: (city and either US State, if applicable, or country)	Framingham, Massachusetts
VIII-4-1 -2-3	Mailing address:	16R Hodder Lane
VIII-4-1 -2-4	Citizenship:	US
VIII-4-1 -2-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	<i>Marshall Morningstar</i>
VIII-4-1 -2-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	<i>January 20, 2003</i>
VIII-4-1 -3-1	Name:	KAKUSHIMA, Masatoshi
VIII-4-1 -3-2	Residence: (city and either US State, if applicable, or country)	Yokohama-shi, Japan
VIII-4-1 -3-3	Mailing address:	13-12, Shin-ishikawa 2-chome, Aoba-ku
VIII-4-1 -3-4	Citizenship:	JP
VIII-4-1 -3-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1 -3-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

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PCT REQUEST

0485-0225FPC

Original (for SUBMISSION) - printed on 15.01.2003 11:16:16 AM

VIII-4-1 -2-1	Name:	MORNINGSTAR, Marshall
VIII-4-1 -2-2	Residence: (city and either US State, if applicable, or country)	Framingham, Massachusetts
VIII-4-1 -2-3	Mailing address:	16R Hodder Lane
VIII-4-1 -2-4	Citizenship:	US
VIII-4-1 -2-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1 -2-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1 -3-1	Name:	KARUSHIMA, Masatoshi
VIII-4-1 -3-2	Residence: (city and either US State, if applicable, or country)	Yokohama-shi, Japan
VIII-4-1 -3-3	Mailing address:	13-12, Shin-ishikawa 2-chome, Aoba-ku
VIII-4-1 -3-4	Citizenship:	JP
VIII-4-1 -3-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	<i>Masatoshi Karushima</i>
VIII-4-1 -3-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	<i>January 24, 2003</i>

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PCT REQUEST

0485-0225FPC

Original (for SUBMISSION) - printed on 15.01.2003 11:16:16 AM

VIII-4-1 -4-1 VIII-4-1 -4-2 VIII-4-1 -4-3 VIII-4-1 -4-4 VIII-4-1 -4-5	Name: Residence: (city and either US State, if applicable, or country) Mailing address: Citizenship: Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent) Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	KAJI, Hidefumi Toda-shi, Japan 3-8-416, Kawagishi 2-chome JP Hidefumi Kaji X January 24, 2003
VIII-4-1 -5-1 VIII-4-1 -5-2 VIII-4-1 -5-3 VIII-4-1 -5-4 VIII-4-1 -5-5	Name: Residence: (city and either US State, if applicable, or country) Mailing address: Citizenship: Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent) Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	KAWAGUCHI, Takayuki Toshima-ku, Japan 24-5-2005, Kita-ohtsuka 2-chome JP Takayuki Kawaguchi January 24, 2003
VIII-4-1 -6-1 VIII-4-1 -6-2 VIII-4-1 -6-3 VIII-4-1 -6-4 VIII-4-1 -6-5	Name: Residence: (city and either US State, if applicable, or country) Mailing address: Citizenship: Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent) Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	KUME, Toshiyuki Saitama-shi, Japan 1151-2, Ooaza-Nakao JP Toshiyuki Kume January 27, 2003

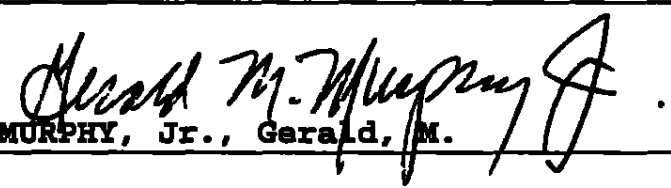
83

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PCT REQUEST

0485-0225FPC

Original (for SUBMISSION) - printed on 06.02.2003 02:53:46 PM

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (Including declaration sheets)	10 GMM	-
IX-2	Description	27	-
IX-3	Claims	5	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	43 GMM	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-9	Original separate power of attorney	✓	-
IX-9	Original separate power of attorney	✓	-
IX-9	Original separate power of attorney	✓	-
IX-9	Original separate power of attorney	✓	-
IX-9	Original separate power of attorney	✓	-
IX-9	Original separate power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	MURPHY, Jr., Gerald, M.	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-1	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/EP
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	
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PCT (ANNEX - FEE CALCULATION SHEET)

0485-0225FPC

Original (for SUBMISSION) - printed on 06.02.2003 02:53:46 PM

(This sheet is not part of and does not count as a sheet of the international application)

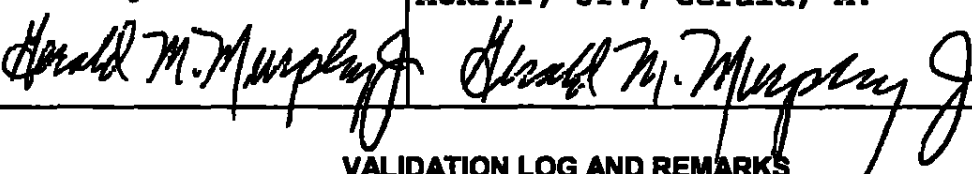
0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	
0-4	Form - PCT/RO/101 (Annex)	
0-4-1	PCT Fee Calculation Sheet Prepared using	PCT-EASY Version 2.92 (updated 01.01.2003)
0-9	Applicant's or agent's file reference	0485-0225FPC
2	Applicant	TANABE SEIYAKU CO., LTD., et al.
12	Calculation of prescribed fees	fee amount/multiplier Total amounts (USD)
12-1	Transmittal fee T	⇒ 240
12-2-1	Search fee S	⇒ 936
12-2-2	International search to be carried out by	EP
	International fee	
	Basic fee (first 30 sheets) b1	407
12-4	Remaining sheets	213 GMM
12-5	Additional amount (X) 9	
12-6	Total additional amount b2	117 108 GMM
12-7	b1 + b2 = B	524 525 GMM
12-8	Designation fees	
	Number of designations contained in international application	94
12-9	Number of designation fees payable (maximum 5)	5
12-10	Amount of designation fee (X) 88	
12-11	Total designation fees D	440
12-12	PCT-EASY fee reduction R	-125
12-13	Total international fee (B+D-R) I	⇒ 839 820 GMM
12-14	TOTAL FEES PAYABLE (T+S+H+P)	⇒ 2,015 2,006 GMM
12-19	Mode of payment	cheque
12-20	Deposit account instructions	
	The receiving Office:	United States Patent and Trademark Office (USPTO) (RO/US)
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓
12-21	Deposit account No.	02-2448
12-22	Date	06 February 2003 (06.02.2003)

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PCT (ANNEX - FEE CALCULATION SHEET)

0485-0225FPC

Original (for SUBMISSION) - printed on 08.02.2003 02:53:46 PM

12-23	Name and signature	MURPHY, Jr., Gerald, M. 
-------	--------------------	---

VALIDATION LOG AND REMARKS

13-2-3	Validation messages Names	Green? Agent 1.: Last name should preferably be entered in capital letters. Please verify.
13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.

INTERNATIONAL SEARCH REPORT

PCT/US 03/03449

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/4188 A61P29/00 //(C07D487/04,235:00,
209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 30781 A (TANABE SEIYAKU) 3 May 2001 (2001-05-03) claims 1,17	1,16,18, 19

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another claim or other special reason (as specified)

"O" document relating 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 contact with the application but cited to understand the principles 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

"8" document member of the same patent family

Date of the actual completion of the international search

20 May 2003

Date of mailing of the international search report

03/06/2003

Name and mailing address of the ISA

European Patent Office, P.O. Box 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 661 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Alfaro Faus, I

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/03449

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 15 - 22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ 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.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

Int.

PCT/US 03/03449

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0130781	A	03-05-2001	
		AU 1437001 A	08-05-2001
		BR 0014651 A	18-06-2002
		CA 2388639 A1	03-05-2001
		CN 1382143 T	27-11-2002
		EP 1307455 A2	07-05-2003
		JP 2003512468 T	02-04-2003
		WO 0130781 A2	03-05-2001

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 0485-0225FPC	
International application No. PCT/US03/03449	International filing date (day/month/year) 06 February 2003	(Earliest) Priority date (day/month/year) 07 February 2002	
Title of invention INHIBITORS OF $\alpha_L \beta_2$ INTEGRIN MEDIATED CELL ADHESION			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) TANABE SEIYAKU CO., LTD. 2-10 Doshomachi 3-chome Chuo-ku, Osaka 541-8505 Japan		Telephone No. 011-81-6-6300-2728	
		Facsimile No. 011-81-6-6300-2695	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: JP		State (that is, country) of residence: JP	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) SIRCAR, Ila 4832 Riding Ridge Road San Diego, CA 92130 United States of America			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) MORNINGSTAR, Marshall 16R Hodder Lane Framingham, MA 01702 United States of America			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
☒ Further applicants are indicated on a continuation sheet.			

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Sheet No. 2.

International application No.
PCT/US03/03449

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)
KAKUSHIMA, Masatoshi
13-12, Shin-ishikawa 2-chome, Aoba-ku
Yokohama-shi, Kanagawa 225-0003
Japan

State (that is, country) of nationality:
JP

State (that is, country) of residence:
JP

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)
KAJI, Hidefumi
3-8-416, Kawagishi 2-chome
Toda-shi, Saitama 335-0015
Japan

State (that is, country) of nationality:
JP

State (that is, country) of residence:
JP

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)
KAWAGUCHI, Takayuki
24-5-2005, Kita-ohtsuka 2-chome
Toshima-ku, Tokyo 170-0004
Japan

State (that is, country) of nationality:
JP

State (that is, country) of residence:
JP

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)
KUME, Toshiyuki
1151-2, Ooaza-Nakao
Saitama-shi, Saitama 336-0932
Japan

State (that is, country) of nationality:
JP

State (that is, country) of residence:
JP

☐ Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)MURPHY, Jr., Gerald M.
BIRCH, STEWART, KOLASCH & BIRCH, LLP
P.O. Box 747
Falls Church, VA 22040-0747
United States of America

Telephone No.

703-205-8000

Facsimile No.

703-205-8050

Teleprinter No.

Agent's registration No. with the Office

28,977

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☒ as originally filed☐ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☒ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Languages for the purposes of international preliminary examination: English☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

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Sheet No. 4.

International application No.
PCT/US03/03449

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary
Examining Authority use only

received not received

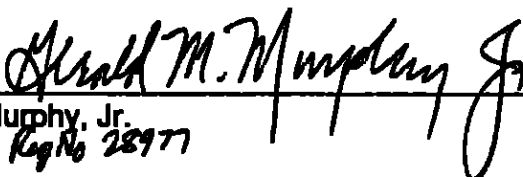
- | | |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listings in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to sequence listings |
| 4. ☐ copy of general power of attorney; reference number, if any: | 8. ☒ other (specify): EPO Deposit Account Form |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).


Gerald M. Murphy, Jr.
Reg No 28977

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

95
95

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US03/03449		For International Preliminary Examining Authority use only	
Applicant's or agent's file reference 0485-0225FPC		Date stamp of the IPEA	
Applicant TANABE SEIYAKU CO., LTD.			
CALCULATION OF PRESCRIBED FEES			
1. Preliminary examination fee		1530 EUR	P
2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>)		159 EUR	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box		1689 EUR	
		TOTAL	
MODE OF PAYMENT			
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash		
☐ cheque	☐ revenue stamps		
☐ postal money order	☐ coupons		
☐ bank draft	☐ other (specify):		
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPEAs)			
☒ Authorization to charge the total fees indicated above.		IPEA/ EP	
☐ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.		Deposit Account No.: 28300323	
		Date: 9 July 2003	
		Name: Gerald M. Murphy, Jr.	
		Signature: Gerald M. Murphy Jr.	

Payment of fees and costs

**Directorate
Cash and Accounts
D – 80298 München**

Please complete using a typewriter or a word processor

Name of payer
Gerald M. Murphy, Jr.
BIRCH, STEWART, KOLASCH & BIRCH, LLP
Address
P. O. Box 747
Falls Church, Virginia 22040-0747
United States of America

Payer's reference
0485-0225FPC

Mode of payment ☐ Bank/Giro transfer ^① ☐ Enclosed Cheque No. ☒ Debit from deposit account ^①	Bank/Giro Office Deposit account No. 28300323
--	--

**Purpose of
payment**

Patent application / Patent No. (A separate form is required for each application)			
EP		PCT	US03/03449

Explanations:

1) Payment must be made without charge to the payee. For European Patent Organisation accounts and corresponding currencies of payment see overleaf.

2) Debits from deposit accounts with the EPO may only be made in DEM or, from 2 March 1998, in EUR.

3) Payments must be made in the currency of the State in which the EPO account in question is held. Please use the abbreviations for currencies of payment shown overleaf.

4) Contracting States should only be specified if they differ from those crossed in box 32.2 of EPO Form 1001 (Request for Grant) or in box V of PCT Form RP/101.

When extension fees are paid, the States for which they are intended must be specified.

Code		Currency ^②	Amount
001	Filing fee		
002	Search fee		
005	Designation fee(s) ①		
015	Claims fee(s) (Rule 31 (1) EPC)		
055	Additional copy		
008	Examination fee		
007	Fee for grant including fee for printing (up to 35 pages)		
008	Additional fee for printing (more than 35 pages)		
033	Renewal fee for the 3rd year		
034	Renewal fee for the 4th year		
035	Renewal fee for the 5th year		
	Extension fee(s) for ①: _____		
	<u>Preliminary Exam Fee</u>	EUR	1530
	<u>Handling Fee</u>	EUR	159

	Total	EUR	1689

Total

Signature

Gerald M. Murphy, Jr.

Place, Date **Falls Church, Virginia**
United States of America

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B.S.K.B. LLP

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MURPHY, Gerald M.
BIRCH, STEWART, KOLASCH & BIRCH LLP
P.O. Box 747
Falls Church, VA 22040-0747
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year) 11/08/2003

Applicant's or agent's file reference
0485-0225FPC

IMPORTANT NOTIFICATION

International application No.

PCT/US 03/ 03449

International filing date (day/month/year)

06/02/2003

Priority date (day/month/year)

07/02/2002

Applicant

TANABE SEIYAKU CO., LTD. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

FERRO VASCONCELOS M
Tel. (+49-89) 2399 2828



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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference 0485-0225FPC	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/16)	
International application No. PCT/US 03/ 03449	International filing date (day/month/year) 06/02/2003	Priority date (day/month/year) 07/02/2002
International Patent Classification (IPC) or national classification and IPC C07D487/04		
Applicant TANABE SEIYAKU CO., LTD. et al.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 2 sheets, including this cover sheet.
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

- This report contains indications relating to the following items:
 - ☒ Basis of the report
 - ☐ Priority
 - ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - ☐ Lack of unity of invention
 - ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - ☐ Certain documents cited
 - ☐ Certain defects in the international application
 - ☐ Certain observations on the international application

Date of submission of the demand 18/07/2003	Date of completion of this report 06/08/2003
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer VERHULST W Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)



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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US 03/03449

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(a) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in the independent claims, which have been the subject of an international search report, meets the criteria mentioned in Article 33(1) PCT, i.e. appears to be novel, to involve an inventive step and to be industrially applicable.

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From the INTERNATIONAL SEARCHING AUTHORITY

To:
BIRCH, STEWART, KOLASCH & BIRCH LLP
Attn. Murphy, Gerald M.
P.O. Box 747
Falls Church, VA 22040-0747
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Docketed

08-02-03

Date of mailing (day/month/year)	03/06/2003
Applicant's or agent's file reference	0485-0225FPC
FOR FURTHER ACTION	See paragraphs 1 and 4 below
International application No.	PCT/US 03/ 03449
International filing date (day/month/year)	06/02/2003
Applicant TANABE SEIYAKU CO., LTD.	

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.
Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 48):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for International publication.

Within 19 months from the priority date, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl,
Fax (+31-70) 340-3018

Authorized officer

John De Bruijn

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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the letter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 18 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 48.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 18, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 0485-0225FPC	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/US 03/ 03449	International filing date (day/month/year) 06/02/2003	(Earliest) Priority Date (day/month/year) 07/02/2002
Applicant TANABE SEIYAKU CO., LTD.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

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101/03 03/03443

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D487/04 A61K31/4188 A61P29/00 //(C07D487/04,235:00,209:00)		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) WPI Data, EPO-Internal, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 30781 A (TANABE SEIYAKU) 3 May 2001 (2001-05-03) claims 1,17	1,16,18,19
☐ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family		
Date of the actual completion of the international search 20 May 2003		Date of mailing of the international search report 03/06/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl Fax: (+31-70) 340-3018		Authorized officer Alfaro Faus, I

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INTERNATIONAL SEARCH REPORT

PCT/US 03/03449

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 15 - 22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ 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.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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PCT/US 03/03449

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0130781	A	03-05-2001	AU 1437001 A 08-05-2001
		BR 0014651 A 18-06-2002	
		CA 2388639 A1 03-05-2001	
		CN 1382143 T 27-11-2002	
		EP 1307455 A2 07-05-2003	
		JP 2003512468 T 02-04-2003	
		WO 0130781 A2 03-05-2001	

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PATENT COOPERATION TREATY

WO 03/066636
PCT/US03/03449

Corrected Version / Version corrigée

From the INTERNATIONAL BUREAU

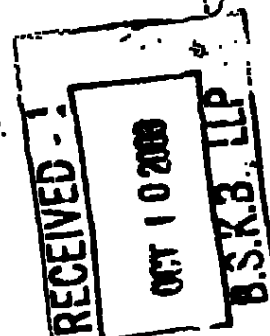
PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

MURPHY, Jr., Gerald, M.
Birch, Stewart, Kolasch & Birch, LLP.
P.O. Box 747
Falls Church, VA 22040-0747
ETATS-UNIS D'AMERIQUE



Date of mailing(day/month/year) 14 August 2003 (14.08.03)		
Applicant's or agent's file reference 0485-0225FPC		
IMPORTANT NOTICE		
International application No. PCT/US03/03449	International filing date(day/month/year) 06 February 2003 (06.02.03)	Priority date(day/month/year) 07 February 2002 (07.02.02)
Applicant TANABE SEYAKU CO., LTD.		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

AU, AZ, BY, CH, CN, CO, DE, DZ, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

In accordance with Rule 47.1(c), third sentence, 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).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DK, DM, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 14 August 2003 (14.08.03) under No. 03/066636

4. TIME LIMITS for filing a demand for international preliminary examination and for 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, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(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*, 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>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. 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).

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

Authorized officer

Judith Zahra

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

MURPHY, Jr., Gerald, M.
Birch, Stewart, Kolasch & Birch, LLP.
P.O. Box 747
Falls Church, VA 22040-0747
ETATS-UNIS D'AMERIQUE

Date of mailing(day/month/year)

14 August 2003 (14.08.03)

Applicant's or agent's file reference

0485-0225FPC

IMPORTANT NOTICE

International application No.

PCT/US03/03449

International filing date(day/month/year)

06 February 2003 (06.02.03)

Priority date(day/month/year)

07 February 2002 (07.02.02)

Applicant

TANABE SEIYAKU CO., LTD.

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 30, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

None

In accordance with Rule 47.1(c), third sentence, 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).

2. The following designated Offices have waived the requirement for such a communication at this time:

None

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 14 August 2003 (14.08.03) under No. 03/068836

4. **TIME LIMITS for filing a demand for international preliminary examination and for 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, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(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*, 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>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. 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).

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

Authorized officer

Judith Zahra

Facsimile No.(41-22) 740.14.35

Telephone No.(41-22) 338.91.11

409
109

NIT : 900174099-2

SUPERINDUSTRIA Y COMERCIO

Radicación : 04076121 00000000 Folios: 109
Fecha (RFB): 2004-08-05 15:17:40
Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 01 - 42,493
FECHA : AGOSTO 5 DE 2004

******* CONSIGNACION *******

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
PARRA RODRIGUEZ & CA	VELOCIDAD	BANCO POPULAR	050-00110-A	21078787	04/08/2004	844,000.00

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

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
	TOTAL :	\$ 422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

2
110

SUPERINDUSTRIA Y COMERCIO
Radicación : 04076121 00000000 Folios: 109
Fecha (ORD): 2004-05-05 15:17:48
Trámite : 011 PCT-PATENT 379 FREE NRCJ 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION MODELO DE UTILIDAD	()	(✓)
- Indicación de que se solicita la concesión de una patente.	()	(✓)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	(✓)
- Descripción de la invención.	()	(✓)
- Dibujos de ser estos pertinentes.	()	(✓)
- Comprobante de Pago de las tasas establecidas.		
COMPLETA () INCOMPLETA ()		
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA () INCOMPLETA ()		
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA () INCOMPLETA ()		

Firma Responsable: Carla M Nueva

Fecha:

2020
Bogotá, D.C.,

Doctor:
ERNESTO CAVELIER FRANCO
Apoderado
TANABE SEIYAKU CO., LTD.

Oficio N° 03430

ASUNTO:	Radicación N°	04-76121
	Solicitud internacional	PCT/US2003/03449
	Fecha inicio fase nacional	07/09/2004
	Trámite	011
	Evento	379
	Actuación	416
	Folios	001

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:

- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

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 Única N° 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, 10 de 2004

202047

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Conmutador: 3 820840 Fax: 3 505220
Sede CAN: Tr. 40A No. 38-50 3153265 al 69
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