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

(57) Abstract: The present invention relates to a compound of formula (I): wherein R is hydrogen atom, hydroxyl group or carboxamoyl group, and n is 1 or 2, or a pharmaceutically acceptable salt thereof.
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 $\beta_2$ (CD18) integrin subfamily has four members, each consisting of a related but distinct $\alpha$-chain noncovalently paired with CD18: $\alpha_4\beta_2$ integrin (LFA-1, CD11a/CD18), $\alpha_5\beta_2$ integrin (Mac-1, CD11b/CD18), $\alpha_x\beta_2$ integrin (p150/95, CD11c/CD18), and $\alpha_9\beta_2$ 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)).
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 $\alpha_4\beta_2$ integrin for all transplantations.

**SUMMARY OF THE INVENTION**

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

![Chemical structure](image)

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**
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.

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.

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 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.

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 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;

(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.
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); Ohmacht Jr. et al., Ann. Rep. Med. Chem., 33, 71-80 (1998)). Thus the compounds of the present invention have 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
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 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 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 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 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 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 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 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 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 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, 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, 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...
inflammatory conditions, inflammatory bowel diseases (Crohn's disease and ulcerative colitis), cystitis, gastric disorder, regional enteritis, Sjogren's Syndrome, and other autoimmune diseases.

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.

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 disease).

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.

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

Method A:

Among the compounds of the present invention, a compound of formula (I-a):
wherein \( n \) is the same as defined above, or a pharmaceutically acceptable salt thereof, can be prepared by condensing a compound of formula (II):

\[
\text{NC-} \quad \text{H} \quad \text{H-N-} \quad \text{N-} \quad \text{O} \quad \text{N} \quad \text{O} \quad \text{NC}
\]

\[
\text{(I-a)}
\]

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

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

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.

The salt of compounds (II) and (III-a) may be, for example, a salt with an inorganic or organic acid (e.g., trifluoroacetate, hydrochloride, sulfate), or a salt 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 calcium salt).

The condensation reaction of the compound (II) or a salt thereof with the compound (III-a) or a salt thereof can be 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, Et$_3$N), 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., Na$_2$CO$_3$, K$_2$CO$_3$), an alkali metal hydrogen carbonate (e.g., NaHCO$_3$, KHCO$_3$), 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$_2$Cl$_2$), ethers (e.g., diethyl ether, THF, DME, dioxane), amides (e.g., DMF, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), CH$_3$CN, DMSO, and H$_2$O, 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 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 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, Et$_3$N), 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., Na$_2$CO$_3$, K$_2$CO$_3$), an alkali metal hydrogen carbonate (e.g., NaHCO$_3$, KHCO$_3$), 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., CHCl₃, CH₂Cl₂), ethers (e.g., diethyl ether, THF, dioxane), amides (e.g., DMF, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), CH₃CN, DMSO, and H₂O, and a mixture of these solvents.

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

Method B:

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

![Chemical Structure](I-b)

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):

\[ R^O-(CH₂)ₙ-COOH \] (III-b)

wherein \( R^O \) 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.

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 selected from conventional protecting groups for a hydroxyl
group which can be easily removed by a conventional method. Examples of such protecting groups include a trialkylsilyl group (e.g., trimethyloxysilyl group, triethyloxysilyl group, and t-butyldimethyloxysilyl group), a benzyl group, a methyl group and a tetrahydropyranyl group.

The condensation reaction of compound (II) or a salt thereof with compound (III-b) wherein R^3O is a protected hydroxyl group, a salt thereof or a reactive derivative thereof can be carried out in a similar procedure as described 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.

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.

The acid treatment can be carried out by using an inorganic acid or an organic acid such as hydrochloride, hydrobromide, acetic acid, p-toluenesulfonylic 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., 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 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.
The treatment with BBr₃ for the demethylation can be carried out in a suitable solvent (e.g., THF, CH₂Cl₂, AcOH) at a temperature of −78 °C to 50 °C.

In case that compound (III-b) wherein R²O 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, triethyldimethylsilyl 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., CHCl₃, CH₂Cl₂), ethers (e.g., diethyl ether, THF, DME, dioxane), amides (e.g., DMF, N-methylpyrrolidone), ketones (e.g., acetone, methyl ethyl ketone), CH₃CN, 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):

\[ \text{(I-c)} \]
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):

\[ \text{H}_2\text{NC}(-\text{O})-(\text{CH}_2)_n\text{-COOH (III-c)} \]

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 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 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:

Scheme 1.
(In the above scheme, X is a C\textsubscript{1-6} alkyl group or a benzyl group, and tBDMSO is tert-butyldimethylsilyloxy group.)

Step (a): Compound (IV) can be prepared by reacting 4-hydroxyproline C\textsubscript{1-6} 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., Et\textsubscript{3}N, DIEA) and pyridine, and conventional inorganic bases such as an alkali metal hydrocarbonate (e.g., NaHCO\textsubscript{3}, KHCO\textsubscript{3}) and an alkali metal carbonate (e.g., Na\textsubscript{2}CO\textsubscript{3}, K\textsubscript{2}CO\textsubscript{3}).

The solvent can be selected from any one which does not disturb the condensation reaction, for example, CH\textsubscript{2}Cl\textsubscript{2}, 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 CH$_3$CN. 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., K$_2$CO$_3$, Na$_2$CO$_3$) and an alkali metal hydrocarbonate (e.g., NaHCO$_3$), and conventional organic bases such as pyridine, DMAP, Et$_3$N, and DIEA.

The solvent can be selected from any one which does not disturb the cyclization reaction, for example, toluene, DME, CH$_3$Cl$_2$, THF, CH$_3$CN, DMF, alcohols (e.g., MeOH, EtOH) or a 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):

\[
\text{CN} \quad \text{CH}_2\text{-Y} \quad (\text{XI})
\]

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, 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 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 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 (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 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 (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.
The solvent can be selected from any one which does not disturb the reaction, for example, CH₂Cl₂, THF, DMF, CH₃CN, and toluene.

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, PtO₂) in a suitable solvent under a H₂ atmosphere at room temperature.

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 C₁₋₆ alkyl group means a straight chain or branched chain alkyl group 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

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

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 µL) in THF (5 mL) was stirred overnight at room temperature. The reaction mixture was 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⁺).

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 µL) in THF (5 mL) was stirred overnight at room temperature. The reaction mixture was evaporated. The residue was dissolved in EtOAc and the 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

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-
dione (0.300 g), 3-methoxypropionic acid (0.209 µL), EDC (0.224 g), HOBT (0.221 g) and DIEA (0.38 µL) in THF (15 mL) was stirred overnight at room temperature. The reaction mixture was evaporated. 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 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 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+).

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 µL) in THF (4 mL) was added a solution of benzzyloxyacetyl chloride (57 µL) 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$_2$SO$_4$), filtered and concentrated. The residue was purified by HPLC (Beckman 5 μ C18 column; eluted with a gradient of 5 H$_2$O/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$_2$SO$_4$) 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 H$_2$O/MeCN (10-100%)/0.1% TFA) to give 0.023 g of the titled compound. MS (m/z) 473 [MH$^+$] and 495 [MNa$^+$].

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

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

Scheme 2
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 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 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 trituated 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 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 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).

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 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-dionä. Diastereomer A: 7.46 g, MS: m/z 415 (M⁺); and 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-
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-
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 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 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-butyldimethylsilyloxy)-1,3-diazabicyclo[3.3.0]octane-2,4-dione.
(5S, 7R) isomer: 7.6 g, MS: m/z 530 (M⁺); and
(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-butyldimethylsilyloxy)-1,3-diazabicyclo[3.3.0]octane-2,4-dione (1.0 g) in THF (1 mL) was 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 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) 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 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 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 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 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 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

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-
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
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
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
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
2.5x10^6/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 MgCl_2,
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-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 the 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):

\[
\text{NC} \quad \text{R} \quad \text{HN} \quad \text{O} \\
\text{Cl} \quad \text{Cl}
\]

(I)

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.

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 carbamoyl group.

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

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.

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 carbamoyl group and n is 2.
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):

\[
\begin{array}{c}
\text{NC} \\
\text{H} \\
\text{H} \\
\text{N} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{Cl} \\
\text{Cl} \\
\text{Cl} \\
\end{array}
\quad (I-a)
\]

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

\[
\begin{array}{c}
\text{NC} \\
\text{H}_2\text{N} \\
\text{N} \\
\text{O} \\
\text{O} \\
\text{Cl} \\
\text{Cl} \\
\end{array}
\quad (II)
\]

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

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

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):

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

\[ R^1O-(CH_2)_n-COOH \] (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 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):

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-c):
\[ \text{H}_2\text{N} = \text{O} - (\text{CH}_2)_n - \text{COOH} \] (III-c)
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.

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

15. A method for treatment or prevention of a LFA-1 mediated 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 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 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.
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 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, 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 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 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 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, and gastric disorder.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/4188 A61P29/00 //C07D487/04, 23D:00, 209:00)

According to International Patent Classification (IPC) or to both regional 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

WPI Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>WO 01 30781 A (TANABE SEIYAKU) 3 May 2001 (2001-05-03) claims 1,17</td>
<td>1,16,18, 19</td>
</tr>
</tbody>
</table>

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 published on or after the international filing date
  *L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another publication or other special reasons (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

Date of the actual completion of the international search: 20 May 2003

Date of mailing of the international search report: 03/06/2003

Names and mailing address of the ISA:
European Patent Office, P.B. 5616 Patentlaan 2 NL – 2280 HV Rijswijk
Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax. (+31–70) 340–0016

Authorized officer: Alfaro Faus, I
INTERNATIONAL SEARCH REPORT

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.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO 0130781 A</td>
<td>03-05-2001</td>
<td>AU 1437001 A</td>
<td>08-05-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 0014651 A</td>
<td>18-06-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2388639 A1</td>
<td>03-05-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1382143 T</td>
<td>27-11-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1307455 A2</td>
<td>07-05-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2003512468 T</td>
<td>02-04-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 0130781 A2</td>
<td>03-05-2001</td>
</tr>
</tbody>
</table>