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(71) Applicant *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: TERASAKA, Tadashi [JP/JP]; A-201, 4-7-21, Hata, Ikeda-shi, Osaka 563-0021 (JP). NAKAMURA, Katsuya [JP/JP]; 2-12-1-103, Kamihamuro, Takatsuki-shi, Osaka 569-1104 (JP). SEKI, Nobuo [JP/JP]; 6-6-15, Nakayamasakuradai, Takarazuka-shi, Hyogo 665-0877 (JP). KUNO, Masako [JP/JP]; 1-207-603, Higashisonoda-cho, Amagasaki-shi, Hyogo 661-0953 (JP). TSUJIMOTO, Susumu [JP/JP]; 2-3-25, Nishikomuro, Fujiidera-shi, Osaka 583-0018 (JP). SATO, Akihiro [JP/JP]; 1-5-16, Oguradai, Kita-ku, Kobe-shi, Hyogo 651-1211 (JP). NAKANISHI, Isao [JP/JP]; 319-1, Tainosho-cho, Tenri-shi, Nara 632-0071 (JP). KINOSHITA, Takayoshi [JP/JP]; 2-495-1-1002, Izumi-machi, Daito-shi, Osaka 574-0024 (JP). NISHIO, Nobuya [JP/JP]; 4-24-406, Misono-cho, Kawanishi-shi, Hyogo 666-0013 (JP). OKUMURA, Hiroyuki [JP/JP]; 4-31-2, Shinkofudai, Toyono-cho, Toyono-gun, Osaka 563-0105 (JP). TSUJI, Kiyoshi [JP/JP]; 170, Hata-cho, Kishiwada-shi, Osaka 596-0831 (JP).

(74) Agent: SHIMIZU, Hatsushi; Kantetsu Tsukuba Building 6F, 1-1-1, Oroshi-machi, Tsuchiura-shi, Ibaraki 300-0847 (JP).

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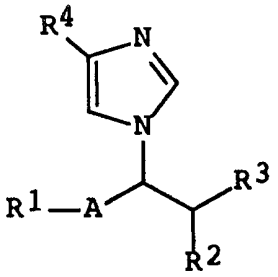
(54) Title: IMIDAZOLE COMPOUNDS AND THEIR USE AS ADENOSINE DEAMINASE INHIBITORS

(57) Abstract

Imidazole compounds having adenosine deaminase inhibitory activity represented by formula (I) wherein $R^1$ is hydrogen, hydroxy, protected hydroxy, or aryl optionally substituted with suitable substituent (s); $R^2$ is hydrogen or lower alkyl; $R^3$ is hydroxy or protected hydroxy; $R^4$ is cyano, (hydroxy)iminoamino(lower)alkyl, carboxy, protected carboxy, heterocyclic group optionally substituted with amino, or carbamoyl optionally substituted with suitable substituent(s); and –A– is –Q– or –O–Q–, wherein Q is single bond or lower alkylene, provided that when $R^2$ is lower alkyl, then $R^1$ is hydroxy, protected hydroxy, or aryl optionally substituted with suitable substituent(s), its prodrug, or their salt. The compounds are useful for treating and/or preventing diseases for which adenosine is effective.

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# IMIDAZOLE COUMPOUNDS AND THEIR USE AS ADENOSINE DEAMINASE INHIBITORS

## Technical Field

This invention relates to novel imidazole compounds having pharmacological activity, to a process for their production and to a pharmaceutical composition containing the same.

## Background Art

Adenosine (Ado) is an endogenous purine nucleoside released by cells as part of the normal metabolic machinery. Ado has wide variety of biological activities, namely potent antiinflammatory and immunosuppressive properties, protective effects in cardiovascular and cerebrovascular ischemia, anticonvulsant effects and modulation effects of platelet aggregation, lipolysis, glycogenesis, blood flow and neurotransmission. Ado shows the biological activities by binding to its receptors anchored in the cell membrane. Therefore, it is the beneficial treatment for many diseases to perform the pharmacological elevation of extracellular Ado concentrations.

Adenosine deaminase (ADA) catalyzes an essentially irreversible deamination of adenosine or deoxyadenosine to inosine or deoxyinosine, respectively. In the last 10 years, ADA, which was considered to be cytosolic, has been found on the cell surface of many cells. Thus, blocking ADA activity with specific inhibitor is the potent way to elevate Ado concentrations in biological systems and the beneficial treatment for many diseases.

Some compounds have known to have inhibitory activity of ADA (J. Med. Chem. 27, 274-278, 1984; *ibid.* 31, 390-393, 1988; *ibid.* 34, 1187-1192, 1991; *ibid.* 35, 4180-4184, 1992; *ibid.* 37, 305-308, 1994; *ibid.* 37, 3844-3849, 1994; and WO98/02166).

Known imidazole compounds with pharmaceutical activity other

than ADA inhibitory activity are described in U.S. Patent No. 4,451,478 and WO97/26883.

Furthermore, some imidazole derivatives having ADA inhibitory activity have been reported, for example, as described in Drug Developement Reseach 28, 253-258, 1993.

Disclosure of the Invention

This invention relates to novel imidazole compounds, which have pharmaceutical activity such as ADA inhibiting activity, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

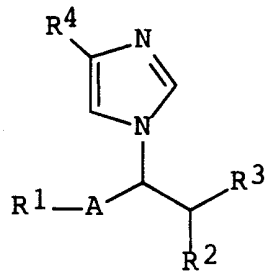
One object of this invention is to provide the novel imidazole compounds, which have an ADA inhibiting activity.

Another object of this invention is to provide a process for production of the imidazole compounds.

A further object of this invention is to provide a pharmaceutical composition containing the imidazole compound as an active ingredient.

Still further object of this invention is to provide a use of the imidazole compound for manufacturing a medicament for treating or preventing various diseases, or a method of treating or preventing various diseases by administering the imidazole compound in an effective amount to elevate adenosine concentration.

The imidazole compounds of this invention can be represented by the following formula (I):



(I)

wherein $R^1$ is hydrogen, hydroxy, protected hydroxy, or aryl optionally substituted with suitable substituent(s);

$R^2$ is hydrogen or lower alkyl;

$R^3$ is hydroxy or protected hydroxy;

$R^4$ is cyano, (hydroxy)iminoamino(lower)alkyl, carboxy, protected carboxy, heterocyclic group optionally substituted with amino, or carbamoyl optionally substituted with suitable substituent(s); and

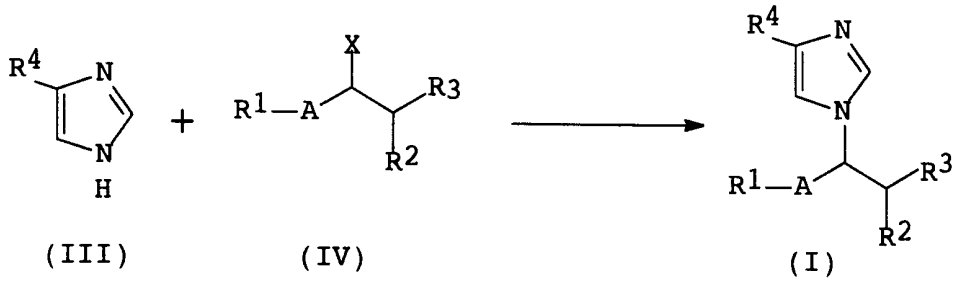
-A- is -Q- or -O-Q-, wherein Q is single bond or lower alkylene,

provided that when $R^2$ is lower alkyl, then $R^1$ is hydroxy, protected hydroxy, or aryl optionally substituted with suitable substituent(s),

its prodrug, or their salt.

The compound (I), its prodrug, or their salt can be prepared by the following processes. In the following formulae, compounds may be prodrugs or their salts.

Process 1



(III) (IV) (I)

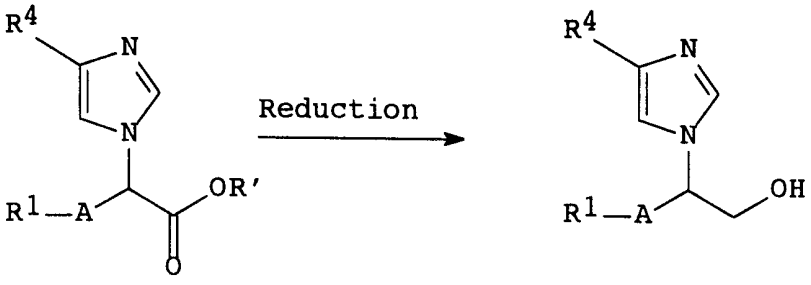
wherein $R^1$, $R^2$, $R^3$, $R^4$, and A are each as defined above, and X is hydroxy or a leaving group, provided that $R^3$ is not hydroxy.

In this process the compound (I) can be produced by reacting the compound (IV), where X is hydroxy, with alkanesulfonyl chloride

(i.e., methanesulfonyl chloride, etc.) or arylsulfonyl chloride (i.e., toluenesulfonyl chloride, etc.) in the presence of a base such as triethylamine or pyridine in a solvent such as dichloromethane, chloroform, tetrahydrofuran, or diethyl ether from 0°C to room temperature for about 1 hour and reacting the resulting sulfonate with the compound (III) in the presence of a base such as sodium hydride, potassium tert-butoxide, or potassium carbonate in a solvent such as dimethylformamide (DMF) from room temperature to 100°C for 5 to 100 hours. Alternatively, the compound (III) can be reacted with the compound (IV) in the presence of a base such as sodium methoxide, potassium tert-butoxide, or sodium hydride to give the compound (I).

The compound (I) wherein $R^3$ is hydroxy can be obtained by the following process:

Process 2




(II) (I-1)

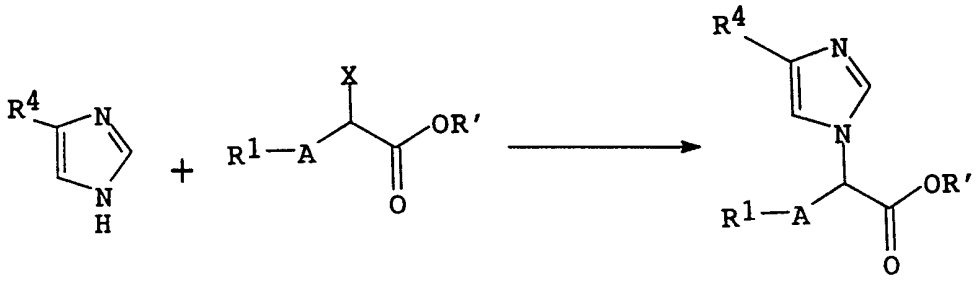
In the reaction formula $R^1$ and $R^4$ are as defined above and R' is a hydroxy protective group.

In process 2, the compound (I-1) can be produced by reducing the compound (II) using a reducing agent such as sodium borohydride in a solvent such as methanol, ethanol, tetrahydrofuran, or water at 0°C to reflux temperature for 30 minutes to 72 hours.

When the compound (I) contains a protected hydroxy group, the protected hydroxy group can be converted to a hydroxy group by a known method, for example, by reacting the compound with a deprotecting agent such as palladium hydroxide on carbon/cyclohexane, iodotrimethylsilane or tetrabutylammonium fluoride in a solvent such as ethanol, chloroform or tetrahydrofuran.

The compound (I) where $R^4$ is (hydroxy)iminoamino(lower)alkyl, heterocyclic group or substituted carbamoyl can be prepared from the compoupd (I) where $R^4$ is cyano or protected carboxy by reacting the latter with the compound corresponding to $R^4$ of the former with or without a condensing agent such as sodium methoxide at room temperature to 120°C for 2 to 72 hours.

The starting compound (II) can be prepared by the following reaction.



(III) (IV-1) (II)

In the reaction formula $R^1$, $R^4$, R', and A are as defined above.

This reaction can be performed in the same manner as in Process 1.

In the following, suitable examples of the definitions to be included within the scope of the invention are explained in detail.

The term "lower" means a group having 1 to 6 carbon atom(s),

unless otherwise provided.

Suitable "lower alkyl" and lower alkyl moiety of "lower alkoxy" include a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, or the like, with methyl being preferred.

Suitable "lower alkylene" may be straight or branched one having 1 to 8 carbon atom(s), such as methylene, ethylene, trimethylene, tetramethylene, pentametylene, hexamethylene, or the like.

Suitable "protected hydroxy" includes lower alkoxy optionally substituted with aryl; acyloxy; or tri(lower)alkylsilyloxy (i.e., trimethylsilyloxy, tert-butyldimethylsilyloxy, etc.); or the like.

Suitable hydroxy protective groups in the protected hydroxy group include lower alkyl optionally substituted with aryl; acyloxy; tri(lower)alkylsilyloxy (i.e., trimethylsilyloxy, tert-butyldimethylsilyloxy, etc.); or the like.

Suitable "halogen" includes fluorine, chlorine, bromine, or iodine.

Suitable "aryl" and aryl moeity of "aroyl" include phenyl, naphthyl, tolyl, xylyl, or the like, with phenyl and naphthyl being preferred.

Suitable "protected carboxy" includes lower alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc.), aryloxy-carbonyl (e.g., phenoxycarbonyl, 4-nitrophenoxycarbonyl, etc.), ar(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, etc.), or the like.

Suitable carboxy protective groups in the protected carboxy group include lower alkyl (e.g., methyl, ethyl, or tert-butyl), halo(lower)alkyl (e.g., 2-iodomethyl or 2,2,2-trichloroethyl), ar(lower)alkyl (e.g., benzyl, trityl, 4-methoxybenzyl, 4-nitrobenzyl, phenethyl, bis(methoxyphenyl)methyl, 3,4-dimethoxybenzyl or 4-hydroxy-3,5-di-tert-butylbenzyl), aryl (e.g.,

phenyl, naphthyl, tolyl, or xylyl), and the like. More suitable examples are lower alkyl such as methyl, ethyl, or tert-butyl, and ar(lower)alkyl such as benzyl.

Suitable "acyl" and acyl moiety of "acyloxy" include lower alkanoyl, aroyl, or the like.

Suitable "lower alkanoyl" includes formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, or the like.

Suitable "aroyl" may be benzoyl, naphthoyl, toluoyl, xyloyl, or the like.

In the definition, unless stated otherwise, "lower alkanoyl" and "aroyl" may be substituted with one or more substituent(s) selected from halogen, cyano, nitro, lower alkyl, and a combination thereof.

Suitable "acyloxy" includes acetyloxy, trifluoroacetyloxy, or the like.

Suitable "leaving group" may be halogen, acyloxy (e.g., acetyloxy, trifluoroacetyloxy, etc.), lower alkylsulfonyloxy (e.g., methanesulfonyloxy, etc.), triarylphosphinoxy (e.g., $-O-P^{+}(C_6H_5)_3$, etc.), or the like.

Suitable "substituent(s)" of "carbamoyl" include amino, hydroxy, lower alkyl, lower alkylsulfonyl, and aminoimino(lower)alkyl optionally substituted with hydroxy, or the like.

Suitable "substituent(s)" of "aryl" include lower alkyl optionally substituted with hydroxy or protected carboxy; lower alkoxy optionally substituted with aryl; hydroxy; amino; acyl; halogen; carboxy; protected carboxy; carbamoyl; lower alkylenedioxy, or the like.

Suitable "heterocyclic group" contains at least one hetero atom selected from nitrogen, sulfur, and oxygen atom and may be saturated or unsaturated, monocyclic or polycyclic heterocyclic group. Preferable examples of the heterocyclic group include N-containing

heterocycyclic group described below.

(1) unsaturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl. pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

(2) saturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g., pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.);

(3) unsaturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,2,4-oxadiazolinyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

(4) saturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., morpholinyl, etc.);

(5) unsaturated 3 to 7-membered, preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), etc.;

(6) saturated 3 to 7-membered preferably 5- or 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiomorpholinyl, thiazolidinyl, etc.) and the like.

Among the above, more preferable heterocyclic group included in $R^4$ is above-mentioned (1), in which the most preferable one is triazolyl or tetrazolyl.

Suitable salts of the compounds of the present invention are

pharmaceutically acceptable conventional non-toxic salts and can be an organic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartarate, oxalate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.), an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. aspartic acid salt, glutamic acid salt, etc.), or the like.

The "prodrug" means the derivatives of compounds of the present invention having a chemically or metabolically degradable group, which becomes pharmaceutically active after biotransformation.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. Furthermore certain compounds of formula (I) which contain alkenyl groups may exist as cis- or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The compound of the formula (I) and its salt can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

The compound of the present invention can be purified by any conventional purification methods employed for purifying organic compounds, such as recrystallization, column chromatography, thin-layer chromatography, high-performance liquid chromatography and the like. The compounds can be identified by conventional methods such as NMR spectrography, mass spectrography, IR spectrography,

elemental analysis, and measurement of melting point.

The compound (I), its prodrug, or their salt can be administered alone or in the form of a mixture, preferably, with a pharmaceutical vehicle or carrier.

The active ingredient of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains a compound (I), as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external (topical), enteral, intravenous, intramuscular, parenteral or intramucous applications. The active ingredient can be formulated, for example, with the conventional non-toxic, pharmaceutically acceptable carriers for ointment, cream, plaster, tablets, pellets, capsules, suppositories, solution (saline, for example), emulsion, suspension (olive oil, for example), aerosols, pills, powders, syrups, injections, troches, cataplasms, aromatic waters, lotions, buccal tablets, sublingual tablets, nasal drops and any other form suitable for use. The carriers which can be used are water, wax, glucose, lactose, gum acacia, gelatin, mannitol, starch paster, magnesium trisilicate, talc, corn starch, keratin, paraffin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active compound is included in a pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the diseases.

The active ingredient can be formulated into, for example, preparations for oral application, preparations for injection, preparations for external application, preparations for inhalation, preparations for application to mucous membranes.

Mammals which may be treated by the present invention include

livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and humans, preferably humans.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose to a human patient of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg, and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

The compound (I) or its pharmaceutically acceptable salts of this invention possesses ADA inhibiting activity and are thus useful in immunomodulation, especially immunosuppression, antiinflammation and treatment and prevention of various diseases for which Ado is effective. Examples of the diseases are as follows:

a) Autoimmune diseases and inflammatory conditions, e.g., various pains collagen diseases, autoimmune diseases, various immunity diseases, and the like in human beings or animals, and more particularly for the treating and/or preventing inflammation and pain in joint and muscle (e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, etc.), inflammatory skin condition (e.g. sunburn, eczema, etc.), inflammatory eye condition (e.g. conjunctivitis, etc.), lung disorder in which inflammation is involved (e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.), condition of the gastrointestinal tract associated with inflammation (e.g. aphthous ulcer, Crohn's disease, atrophic gastritis, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.), gingivitis, (inflammation, pain and tumescence after operation or injury), pyrexia, pain and other conditions associated with inflammation, systemic lupus erythematosus, scleroderma, polymyositis, polychondritis, periarteritis nodosa, ankylosing spondylitis,

inflammatory chronic renal condition (e.g. nephrotic syndrome, glomerulonephritis, membranous nephritis, etc.), acute nephritis, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, dermatomyositis, chronic active hepatitis, acute hepatitis, myasthenia gravis, idiopathic sprue, Grave's disease, multiple sclerosis, primary billiary cirrhoris, Reiter's syndrome, autoimmune hematological disorders (e.g. hemolytic anemia, pure red cell anemia, idiopathic thrombocytopenia; aplastic anemia, etc.), myasthenia gravis, uveitis, contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Wegner's granulomatosis, Hodgkin's disease, or the like;

b) Organ or tissue allo-or xeno-transplant rejection, e.g., kidney, liver, heart, lung, combined heart-lung, bone marrow, islet cells, pancreatic, skin, chromaffin or dopamine producing cells, small bowel, or corneal transplantation. Treating and/or preventing graft-versus-host disease, such as occurs following bone marrow transplantation;

c) Various leukemias, including virus induced, or various induced lymphomas; and

d) Diseases that arise from, or are aggravated by, insufficient blood flow through a particular organ or portion thereof, e.g., heart attacks or strokes, the microvascular disease of diabetes mellitus, atherosclerosis, or events resulting in a less prolonged loss of blood flow (e.g., angina pectoris, transient ischemic attacks, bowel ischemia, kidney ischemia, intermittant claudication of skeletal muscle, migraine headaches, Raynaud's phenomenon), or the like.

Any patents, patent applications, and publications cited herein are incorporated by reference.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of the compound (I) are shown in

the following.

Adenosine Deaminase (ADA) Enzyme Assay

Test Compound:

1-(1-Hydroxy-4-phenyl-2-butyl)imidazole-4-carboxamide (Example 1)

Test method:

The reaction velocity (V) is measured by a change in absorbance at 265 nm (A265) resulting from the deamination of adenosine. Human ADA was expressed and purified from ADA-deficient bacterial strain. Reaction mixtures in a total volume of 200 μl contained 25 mU/ml of ADA and varying concentrations of adenosine and test compounds in 10 mM phosphate buffer saline (pH 7.4). The reaction was started by addition of ADA to a mixture of adenosine and test compound. The reaction was followed at room temperature by recording decrease in A265 for 5 minutes in SPECTRAmax 250 (Molecular Devices, USA) to automatically calculate Vmax. The inhibition constant (Ki) values of test compounds were determined by Dixon plot.

Results:

Test Compound: Ki=5.9 μM

Endotoxin-induced Cytokine Production

Test Compound:

1-(1-Hydroxy-4-phenyl-2-butyl)imidazole-4-carboxamide

Test method:

BALB/c mice (male, 7 weeks old) were injected i.v. with 0.1 mg/kg of lipopolysaccharides (LPS) in a total volume of 0.2 ml saline. Heparinized blood samples were taken one hour after LPS injection and plasma was collected by centrifugation. TNF-α (inflammatory

cytokine) and IL-10 (anti-inflammatory cytokine) amounts in plasma were assayed by ELISA. Test compounds were administered 30 minutes before LPS injection.

Results :

| | TNF-α (ng/ml) | IL-10 (pg/ml) |
|---|---|---|
| Vehicle | 4.7 ± 0.4 | 71 ± 9.2 |
| Test Compound (320 mg/kg) | 3.1 ± 0.5 | 137 ± 14 |

Best Mode for Carrying out the Invention

The following Preparation and Examples are given for the purpose of illustrating the present invention in detail, but are not to be construed to limit the scope of the present invention.

Preparation 1

A mixture of methyl 4-imidazolecarboxylate (5.0 g) and ammonium chloride (539 mg) in aqueous 28% $NH_3$ solution (75 ml) was heated at 100℃ in a steel sealed tube for 5.5 hours. After cooling, the reaction mixture was concentrated in vacuo. The residue was stirred in a mixed solvent of acetone, ethanol and water (5:5:1, total 25 ml). The resulting precipitates were collected by filtration and washed with the same mixed solvent, and dried in vacuo to give 4-imidazolecarboxamide (4.63 g) as a white solid.

mp: 211-214℃

IR (KBr): 3500-2600, 1652 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 7.06 (1H, br s), 7.34 (1H, br s), 7.58 (1H, s), 7.69 (1H, s)

MASS: 112 $(M+H)^+$

Preparation 2

Triethylamine (583 mg) was added dropwise to a stirred mixture of ethyl (R)-2-hydroxy-4-phenylbutyrate (1.0 g) and methanesulfonyl chloride (660 mg) in dichloromethane (10 ml) at ice-bath temperature. After 40 minutes, the reaction mixture was partitioned between dichloromethane and water. The organic layer was washed with brine, dried over magnesium sulfate , and concentrated in vacuo to give ethyl (R)-2-methylsulfonyloxy-4-phenylbutyrate (1.37 g) as an oil. This material was used immediately without further purification. NaH (60% in mineral oil, 192 mg) was added to a solution of 4-imidazolecarboxamide (534 mg) in DMF (8 ml) at room temperature. The reaction mixture was stirred for 30 minutes. The methanesulfonate prepared above was added and the resulting mixture was stirred for 3 hours at 60℃.

The reaction mixture was cooled to 10℃ in an ice bath, and the insoluble material was filtered and washed thoroughly with methylene chloride. The filtrate and the washing were combined and then washed with brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel (45 g) chromatography eluting with chloroform/methanol (30:1) to give ethyl 2-(4-carbamoyl-1-imidazolyl)-4-phenylbutyrate (556 mg).

IR (neat): 3500-2800, 1741, 1666 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.26 (3H, t, J=7.1Hz), 2.3-2.68 (4H, m), 4.20 (3H, q, J=7.1Hz), 4.60 (1H, dd, J=9.8, 9.8Hz), 5.44 (1H, br s), 6.96 (1H, br s), 7.08-7.35 (5H, m), 7.46 (1H, s), 7.72 (1H, s)

MASS: 302 $(M+H)^+$

Preparation 3

2-Hydroxyoctanoic acid (1.0 g) was stirred in 10% hydrogen chloride methanol solution (20 ml) at room temperature. After 1.5

hours, the reaction mixture was evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with aqueous $NaHCO_3$ solution and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave methyl 2-hydroxyoctanoate (0.684 g) as a colorless oil.

IR (neat): 3463, 2952, 2927, 2859, 1735 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 0.88 (3H, t, J=6.5Hz), 1.25-1.90 (10H, m), 2.70 (1H, br s), 3.79 (3H, s), 4.19 (1H, br)

MASS: 175 $(M+H)^+$

Preparation 4

The following compounds were obtained according to a similar manner to that of Preparation 2.

(1) Methyl α-(4-carbamoyl-1-imidazolyl)phenylacetate was prepared from methyl mandelate and 4-imidazolecarboxamide obtained in Preparation 1.

IR (KBr): 3500-2800, 1752, 1675 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 3.84 (3H, s), 5.48 (1H, br s), 5.93 (1H, s), 7.06 (1H, br s), 7.24-7.46 (5H, m), 7.60 (1H, s), 7.67 (1H, s)

MASS: 260 $(M+H)^+$

(2) Methyl 2-(4-carbamoyl-1-imidazolyl)octanoate was prepared from 4-imidazolecarboxamide obtained in Preparation 1 and methyl 2-hydroxyoctanate obtained in Preparation 3.

mp: 63.5-65.5℃

IR (KBr): 3400-2800, 1753, 1671 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 0.87 (3H, t, J=6.5Hz), 1.05-1.45 (6H, m), 1.90-2.20 (4H, m), 3.77 (3H, s), 4.71 (1H, dd, J=9.6,

5.6Hz), 5.52 (1H, s), 7.10 (1H, s), 7.59 (1H, s), 7.72 (1H, s)

MASS: 268 $(M+H)^+$

Preparation 5

NaH (60% in mineral oil, 60 mg) was added to a stirred solution of 4-imidazolecarboxamide (obtaiend in Preparation 1) (167 mg) in DMF (3.5 ml), and the reaction mixture was stirred for 1.5 hours at 55℃. Ethyl 2-bromovalerate (0.153 ml) was added to this mixture, and the reaction mixture was stirred for 3 hours at 55-60℃. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel (12 g) chromatography eluting with chloroform/methanol (25:1) to give ethyl 2-(4-carbamoyl-1-imidazolyl)valerate (150 mg).

mp: 95℃

IR (KBr): 3343, 3197, 2964, 1751, 1681 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 0.86 (3H, t, J=7.2Hz), 1.13 (2H, m), 1.20 (3H, t, J=7.1Hz), 2.05 (2H, q, J=7.2Hz), 4.14 (2H, q, J=7.1Hz), 5.16 (1H, t, J=7.2Hz), 7.10 (1H, s), 7.30 (1H, s), 7.73 (1H, s), 7.78 (1H, s)

MASS: 240 $(M+H)^+$

Preparation 6

1-(2-Oxotetrahydrofuran-3-yl)imidazole-4-carboxamide was obtained from 4-imidazolecarboxamide obtained in Preparation 1 and α-bromo-γ-butyrolactone according to a similar manner to that of Preparation 5.

IR (KBr): 3700-3100, 1779, 1745, 1600 $cm^{-1}$

MASS: 196 $(M+H)^+$

Preparation 7

Trifluoromethanesulfonic acid (1.13 g) was added to a stirred mixture of ethyl (S)-(-)-lactate (5.90 g) and benzyl 2,2,2-trichloroacetimidate (15.15 g) in cyclohexane (70 ml) and methylene chloride (35 ml) at room temperature under nitrogen atmosphere. After being stirred for 18 hours, the reaction mixture was filtered. The filtrate was diluted with cyclohexane, and then washed successively with saturated $NaHCO_3$ solution (100 ml) and $H_2O$ (100 ml). The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel (260 g) chromatography eluted with hexane/ethyl acetate (30:1) to give ethyl (S)-2-(benzyloxy)propionate (6.48 g).

IR (neat): 3100-2800, 1743, 1139 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.26 (3H, t, J=7.0Hz), 1.44 (3H, d, J=6.8Hz), 4.05 (1H, q, J=6.8Hz), 4.22 (2H, q, J=7.0Hz), 4.40-4.75 (2H, m), 7.10-7.39 (5H, m)

MASS : 231 $(M+Na)^+$

$[\alpha]^{28.5}$ = -76.0° (C=0.50, EtOH)

Preparation 8

A solution of 1.0M DIBAL (diisobutylaluminum hydride) in hexane (10 ml) was added dropwise to a stirred solution of ethyl (S)-2-(benzyloxy)propionate (obtained in Preparation 7) (2.08 g) in methylene chloride (20 ml) at -78℃ (dry-ice/acetone) for 5 minutes under nitrogen atmosphere. After 20 minutes, methanol (1.6 ml) was added dropwise to the mixture at -78℃, and the resulting mixture was stirred at room temperature for 30 minutes. The mixture was filtered through a pad of Celite, and the solid on the filter was washed with

methylene chloride. The combined filtrates were concentrated in vacuo. The obtained residue was purified by silica gel (35 g) chromatography eluted with hexane/ethyl acetate (30:1) to give (S)-2-(benzyloxy)propionaldehyde (810 mg).

IR (neat): 3100-2800, 1735, 1095 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.33 (3H, d, J=6.9Hz), 3.90 (1H, m), 4.60 (2H, m), 7.10-7.40 (5H, m), 9.67 (1H, s)

MASS: 163 $(M-H)^+$

$[\alpha]^{26.8} = -34.7°$ (C=0.50, EtOH)

Preparation 9

Trimethylsulfoxonium iodide (1.22 g) was added to a stirred suspension of sodium hydride (60% in mineral oil, 234 mg) in dimethylsulfoxide (12 ml) and dimethoxyethane (10 ml) at -3℃ to -4℃ under nitrogen atmosphere. After 10 minutes, a solution of (S)-2-(benzyloxy)propionaldehyde (obtained in Preparation 8)(800 mg) in dimethoxyethane (2 ml) was added dropwise to the mixture for a period of 5 minutes at the same temperature, and the resulting mixture was stirred for 30 minutes at room temperature. The mixture was poured into a cold saturated ammonium chloride solution (50 ml) and extracted with ethyl acetate (100 ml). The organic layer was washed with brine (50 ml), dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel (20 g) chromatography eluted with hexane/ethyl acetate (30:1) to give (3S)-3-benzyloxy-1,2-epoxybutane (507 mg).

IR (neat): 2981, 2927, 2865, 1241, 1103 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.29 (3H, m), 2.40-3.55 (4H, m), 4.50-4.85 (2H, m), 7.10-7.40 (5H, m)

MASS: 201 $(M+Na)^+$

Preparation 10

A solution of 2.0M benzylmagnesium chloride in tetrahydrofuran (2.38 ml) was added dropwise to a stirred mixture of lithium chloride (20.2 mg) and copper(II) chloride (32 mg) in tetrahydrofuran (10 ml) at -78℃ (dry-ice/acetone) for a period of 10 minutes under nitrogen atmosphere. A solution of (3S)-3-benzyloxy-1,2-epoxybutane (obtained in Preparation 9) (425 mg) in tetrahydrofuran (10 ml) was added dropwise to this mixture at -78℃ over 10 minutes. The resulting mixture was stirred at -78℃ for 2.5 hours and then allowed to warm to room temperature, and stirred overnight. The reaction mixture was treated with saturated ammonium chloride solution (20 ml) at an ice-bath temperature, and then diluted with ethyl acetate (100 ml). The organic layer was washed with $H_2O$ (50 ml) and brine (50 ml), dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel (20 g) chromatography eluted with hexane/ethyl acetate (10:1) to give (2S)-2-benzyloxy-5-phenylpentan-3-ol (620 mg).

IR (neat): 3444, 2931, 2865 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.14-2.00 (3H, m), 1.60-1.85 (1H, m), 2.55-3.00 (3H, m), 3.30-3.85 (3H, m), 4.35-4.75 (2H, m), 7.05-7.40 (10H, m)

MASS: 293 $(M+Na)^+$

Preparation 11

The following compounds were obtained according to a similar manner to that of Preparation 10.

(1) (2S)-2-benzyloxy-6-phenylhexan-3-ol was prepared from (3S)-3-benzyloxy-1,2-epoxybutane (obtained in Preparation 9) and phenethylmagnesium chloride.

IR (neat): 3436, 2933, 2861 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.05-1.20 (3H, m), 1.30-2.00 (4H, m), 2.00-2.80 (3H, m), 3.25-3.85 (2H, m), 4.35-4.75 (2H, m), 7.05-7.45 (10H, m)

MASS: 285 $(M+Na)^+$

(2) (2S)-2-benzyloxy-5-(1-naphthyl)pentan-3-ol was prepared from (3S)-3-benzyloxy-1,2-epoxybutane (obtained in Preparation 9) and 1-naphthylmethylmagnesium chloride (J. Am. Chem. Soc. 1943, 65, 295).

IR (neat): 3700-3100, 3100-2800, 1087, 1076 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.10-1.20 (3H, m), 1.75-2.00 (2H, m), 2.15-2.75 (1H, m), 2.95-3.95 (4H, m), 4.40-4.75 (2H, m), 7.20-7.60 (9H, m), 7.65-7.20 (3H, m)

(3) (2S,3S)-2-(benzyloxy)-5-(2-methylphenyl)pentan-3-ol was preparared from the compound obtained in Preparation 9 and 2-methylbenzyl chloride.

NMR ($CDCl_3$, $\delta$): 1.19 (3H, d,J=6Hz), 1.6-1.8 (2H, m), 2.32 (3H, s), 2.64 (1H,d,J=3Hz), 2.6-3.0 (2H,m), 3.3-3.6 (2H,m), 4.43 (1H,d,J=11Hz), 4.67 (1H,d,J=11Hz), 7.1-7.3 (9H, m)

MASS: 307 $(M+Na)^+$

(4) (2S,3S)-2-(benzyloxy)-5-(2-chlorophenyl)pentan-3-ol was prepared from the compound obtained in Preparation 9.

NMR ($CDCl_3$, $\delta$): 1.17 (3H, d,J=5Hz), 1.6-1.9 (2H, m), 2.64 (1H,d,J=3Hz), 2.7-3.1 (2H,m), 3.4-3.5 (2H,m), 4.44 (1H,d,J=12Hz),4.67 (1H,d,J=12Hz), 7.1-7.4 (9H, m)

MASS: 327 $(M+Na)^+$

(5) (2S,3S)-2-(benzyloxy)-5-(2-methoxyphenyl)pentan-3-ol was prepared from the compound obtained in Preparation 9.

NMR ($CDCl_3$, $\delta$): 1.18 (3H, d,J=6Hz), 1.6-1.9 (2H, m), 2.6-3.0 (3H,m), 3.4-3.5 (2H,m), 3.82 (3H,s), 4.44 (1H,d,J=12Hz),4.66 (1H,d,J=12Hz), 6.8-7.0 (2H, m), 7.1-7.4 (7H,m)

MASS: 323 $(M+Na)^+$

(6) (2S,3S)-2-(benzyloxy)-5-(2-hexyloxyphenyl)pentan-3-ol was prepared from the compound obtained in Preparation 9.

NMR ($CDCl_3$, $\delta$): 0.90 (3H,t,J=6Hz), 1.18 (3H, d,J=6Hz), 1.2-1.6 (6H,m), 1.6-1.9 (4H, m), 2.66 (1H,d,J=3Hz), 2.7-2.9 (2H,m), 3.4-3.5 (2H,m), 3.96 (2H,t,J=6Hz), 4.44 (1H,d,J=11Hz),4.66 (1H,d,J=11Hz), 6.8-7.0 (2H, m), 7.1-7.3 (7H,m)

MASS: 393 $(M+Na)^+$

(7) (2S,3S)-2-(benzyloxy)-5-(2,3-dichlorophenyl)pentan-3-ol was prepared from the compound obtained in Preparation 9.

NMR ($CDCl_3$, $\delta$): 1.19 (3H, d,J=5Hz), 1.6-1.9 (2H, m), 2.65 (1H,d,J=3Hz), 2.7-3.1 (2H,m), 3.3-3.5 (2H,m), 4.43 (1H,d,J=11Hz),4.67 (1H,d,J=11Hz), 7.0-7.5 (8H, m)

MASS: 361 $(M+Na)^+$

(8) (2S,3S)-2-(benzyloxy)-5-(2-phenethyloxyphenyl)pentan-3-ol was prepared from the compound obtained in Preparation 9.

NMR ($CDCl_3$, $\delta$): 1.14 (3H, d,J=6Hz), 1.6-1.8 (2H, m), 2.5-3.0 (3H,m), 3.10 (2H,t,J=7Hz), 3.3-3.5 (2H,m), 4.18 (2H,t,J=7Hz), 4.43 (1H,d,J=11Hz), 4.65 (1H,d,J=11Hz), 6.7-7.4 (14H,m)

MASS: 413 $(M+Na)^+$

(9) (2S,3S)-2-(benzyloxy)-5-(2,3-dimethylphenyl)pentan-3-ol was prepared from the compound obtained in Preparation 9.

NMR ($CDCl_3$, $\delta$): 1.19 (3H, d, J=6Hz), 1.6-1.8 (2H, m), 2.22 (3H, s), 2.28 (3H, s), 2.6-3.0 (3H, m), 3.3-3.6 (2H, m), 4.43 (1H, d, J=11Hz), 4.67 (1H, d, J=11Hz), 7.02 (3H, s), 7.2-7.4 (5H, m)

MASS: 321 $(M+Na)^+$

(10) (2S,3S)-2-(benzyloxy)-5-[2,3-(methylenedioxy)phenyl]-pentan-3-ol was prepared from the compound obtained in Preparation 9.

NMR ($CDCl_3$, $\delta$): 1.19 (3H, d, J=6Hz), 1.6-1.9 (2H, m), 2.6-2.9 (3H, m), 3.3-3.5 (2H, m), 4.43 (1H, d, J=12Hz), 4.67 (1H, d, J=12Hz), 5.92 (2H, s), 6.6-6.8 (3H, m), 7.33 (5H, s)

MS: 337 $(M+Na)^+$

Preparation 12

To a stirred solution of $Pd(OAc)_2$ (340 mg), $nBu_3P$ (613 mg), and $Et_3N$ (1.99 g) in DMF (30 ml) was added methyl 2-hydroxy-3-butenoate (1.76 g) followed by 1-iodonaphthalene (5.0 g), and the reaction mixture was stirred at 100℃ for 2.5 hours. The reaction mixture was poured into water (300 ml) and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel (130 g) column chromatography eluting with hexane/ethyl acetate (50:1) to give methyl 4-(1-naphthyl)-2-oxobutyrate (254 mg) as a red oil.

IR (neat): 3050, 2954, 1739, 1725 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 3.25-3.55 (4H, m), 3.86 (3H, s), 7.25-8.10 (7H, m)

Preparation 13

$NaBH_4$ (22 mg) was added portionwise to an ice cooled solution of methyl 4-(1-naphthyl)-2-oxobutyrate (obtained in Preparation 12)

(252.5 mg) in THF(5 ml)-$H_2O$(1 ml). After the addition was completed, the reaction mixture was stirred at ice-bath temperature for 30 minutes. Water (4 ml) was added, and the resulting mixture was stirred for several minutes and then extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel (5 g) column chromatography eluting with hexane/ethyl acetate (10:1) to give methyl 2-hydroxy-4-(1-naphthyl)butyrate (84.4 mg) as a colorless oil.

IR (neat): 3700-3100, 3052, 2954, 1739, 1236, 1103 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 2.03-2.31 (2H, m), 2.91 (1H, d, J=5.2Hz), 3.23 (2H, t, J=7.9Hz), 3.75 (3H, S), 4. 29 (1H, m), 7.30-8.10 (7H, m)

MASS: 245 $(M+H)^+$

Preparation 14

$NaBH_4$ (1.82 g) was added portionwise to an ice cooled solution of ethyl (R)-2-hydroxy-4-phenylbutyrate (2.0 g) in methanol (40 ml). After the addition was completed, the reaction mixture was stirred at room temperature for 45 minutes. Water (20 ml) was added, and the resulting mixture was stirred for several minutes and then evaporated under reduced pressure. The residue was extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure gave (R)-4-phenylbutane-1,2-diol (1.63 g) as a colorless oil. This material was used for the next reaction without further purification.

Imidazole (1.96 g) was added to an ice cooled solution of the diol in DMF (20 ml) followed by tert-butyldimethylsilyl chloride (1.52 g). After 1 hour, the ice-bath was removed and then the mixture was stirred overnight at room temperature.

The reaction mixture was poured into water (200 ml) and

extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel (50 g) column chromatography eluting with hexane/ethyl acetate (50:1) to give (R)-1-(tert-butyldimethylsilyloxy)-4-phenylbutan-2-ol (2.10 g) as a colorless oil.

IR (neat): 3800-3100, 2950, 2931, 2859, 1253, 1116, 1081 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 0.52 (6H, s), 0.90 (9H, s), 1.60-1.85 (2H, m), 2.45 (1H, d, J=3.6Hz), 2.60-2.95 (2H, m), 3.35-3.75 (3H, m), 7.15-7.35 (5H, m)

MASS: 281 $(M+H)^+$

Preparation 15

The following compounds were prepared by a similar procedure to that of Preparation 12.

(1) Methyl 4-(3-methylphenyl)-2-oxobutyrate was prepared as a pale yellow oil from 3-iodotoluene and methyl 2-hydroxy-3-butenoate.

IR (neat): 2954, 2923, 1731, 1238, 1074 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 2.33 (3H, s), 2.92 (2H, t, J=7.5Hz), 3.18 (2H, t, J=7.5Hz), 3.86 (3H, s), 6.90-7.25 (4H, m)

(2) Methyl 4-[3-(trifluoromethyl)phenyl]-2-oxobutyrate was prepared as an oil from 3-iodobenzotrifluoride and methyl 2-hydroxy-3-butenoate.

IR (neat): 2958, 1739, 1728, 1241 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 3.03 (2H, t, J=7.4Hz), 3.22 (2H, t, J=7.4Hz), 3.87 (3H, s), 7.35-7.55 (4H, m)

(3) Methyl 4-[3-(tert-butyldimethylsilyloxy)phenyl]-2-oxobutyrate was prepared as a yellow oil from 3-(tert-

butyldimethylsilyloxy)iodobenzene and methyl 2-hydroxy-3-butenoate.

IR (neat): 2954, 2935, 2857, 1731, 1594, 1244 cm-1

NMR ($CDCl_3$, $\delta$): 0.19 (6H, s), 0.98 (9H, s), 2.90 (2H, t, J=7.6Hz), 3.16 (2H, t, J=7.6Hz), 3.86 (3H, s), 6.65-6.85 (3H, m), 7.15 (1H, m)

MASS: 323 $(M+H)^+$

Preparation 16

The following compounds were prepared by a similar procedure to that of Preparation 13.

(1) Methyl 2-hydroxy-4-(3-methylphenyl)butyrate was prepared as a colorless oil from the compound obtained in Preparation 15(1).

IR (neat): 3700-3100, 3016, 2954, 2859, 1733, 1234, 1099 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.80-2.20 (2H, m), 2.33 (3H, s), 2.65-2.85 (3H, m), 3.76 (3H, s), 4.20 (1H, m), 6.95-7.25 (4H, m)

MASS: 209 $(M+H)^+$

(2) Methyl 2-hydroxy-4-[3-(trifluoromethyl)phenyl]butyrate was prepared from the compound obtained in Preparation 15(2).

IR (neat): 3700-3200, 3016, 2956, 1739, 1328, 1122, 703 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.85-2.25 (2H, m), 2.70-2.95 (3H, m), 3.76 (3H, s), 4.18 (1H, m), 7.35-7.55 (4H, m)

(3) Methyl 2-hydroxy-4-[3-(tert-butyldimethylsilyloxy)-phenyl]butyrate was prepared as a colorless oil from the compound obtained in Preparation 15(3).

IR (neat): 3700-3100, 2954, 2857, 1739, 1595, 1479, 1444, 1273 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 0.19 (6H, s), 0.98 (9H, s), 1.80-2.20 (2H, m), 2.65-2.80 (3H, m), 3.77 (3H, s), 4.18 (1H, m), 6.65-6.90

(3H, m), 7.13 (1H, m)

MASS: 325 $(M+H)^+$

Preparation 17

The following compounds were prepared by a similar procedure to that of Preparation 2.

(1) Methyl 2-(4-carbamoyl-1-imidazolyl)-4-(1-naphthyl)butyrate was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 13.

IR (KBr): 3343, 3185, 1745, 1662 $cm^{-1}$

NMR ($CDCl_3$, $\delta$) 2.40-3.25 (4H, m), 3.73 (3H, m), 4.71 (1H, m), 5.42 (1H, brs), 6.98 (1H, brs), 7.19 (1H, d, J=6.9Hz), 7.35-7.60 (4H, m), 7.74-7.95 (4H, m)

MASS: 338 $(M+H)^+$

(2) Methyl 2-(4-carbamoyl-1-imidazolyl)-4-(3-methylphenyl)-butyrate was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 16(1).

IR (neat): 3800-2800, 1745, 1658 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 2.25-2.75 (7H, m), 3.75 (3H, s), 4.64 (1H, m), 5.43 (1H, br s), 6.85-7.25 (5H, m), 7.45 (1H, s), 7.71 (1H, s)

MASS: 302 $(M+H)^+$

(3) Methyl 2-(4-carbamoyl-1-imidazolyl)-4-[3-(trifluoromethyl)-phenyl]butyrate was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 16(2).

IR (neat): 3700-2800, 1743, 1236 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 2.25-2.80 (4H, m), 3.77 (3H, m), 4.65 (1H, m), 5.43 (1H, br s), 6.96 (1H, br s), 7.20-7.55 (5H, m), 7.73 (1H, s)

MASS: 356 $(M+H)^+$

(4) Methyl 2-(4-carbamoyl-1-imidazolyl)-4-(3-hydroxyphenyl)-butyrate was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 16(3).

IR (neat): 3700-2800, 1745, 1664, 1590, 1267, 1234 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 2.20-2.80 (4H, m), 3.76 (3H, s), 4.65 (1H, m), 5.64 (1H, br s), 6.50-6.85 (3H, m), 6.90-7.30 (2H, m), 7.55 (1H, s), 7.73 (1H, s)

MASS: 304 $(M+H)^+$

Preparation 18

To a stirred solution of $Pd(OAc)_2$ (40 mg, 0.18 mmol), $nBu_3P$ (71 mg, 0.35 mmol), and $Et_3N$ (232 mg, 2.29 mmol) in DMF (5 ml) was added 3-butene-1,2-diol (155 mg, 1.76 mmol) followed by 4-iodotoluene (500 mg, 2.29 mmol), and the reaction mixture was stirred at 100°C for 1.5 h. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate. The organic layer was washed with brine, dried (magnesium sulfate) and evaporated in vacuo. The residue was purified by silica gel (10 g) column chromatography eluting with toluene/ethyl acetate (50:1) to give 1-hydroxy-4-(p-tolyl)butan-2-one (230 mg, 73.4%) as a pale yellow solid.

To an ice cooled solution of 1-hydroxy-4-(p-tolyl)butan-2-one in DMF (5ml) was added imidazole (264 mg, 3.88 mmol) followed by tert-butyldimethylsilyl chloride (234 mg, 1.55 mmol). After 30 minutes the ice-bath was removed and then the mixture was stirred overnight at room temperature. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate. The organic layer was washed with brine, dried (magnesium sulfate), and concentrated in vacuo. The residue was purified by silica gel (8 g) column chromatography eluting with hexane/ethyl acetate (50:1) to give 1-(tert-butyldimethylsilyloxy)-4-(4-methylphenyl)butan-2-one (350

mg, 67.9%) as a colorless oil.

IR (neat): 2933, 2857, 1726, 1255, 1105, 842 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 0.07 (6H, s), 0.91 (9H, s), 2.31 (3H, s), 2.75-2.95 (4H, m), 4.14 (2H, s), 7.08 (4H, s)

Preparation 19

1-(Tert-butyldimethylsilyloxy)-4-[3-(ethoxycarbonyl)-phenyl]butan-2-one (1.62 g, 42.7%) was prepared as a colorless oil by a similar procedure to that of Preparation 18 from ethyl 3-iodobenzoate and 3-butene-1,2-diol.

IR (neat): 2929, 2858, 1720, 1238, 1103 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 0.07 (6H, s), 0.91 (9H, s), 1.40 (3H, t, J=7.1Hz), 2.75-3.05 (4H, m), 4.15 (2H, s), 4.37 (2H, q, J=7.1Hz), 7.30-7.45 (2H, m), 7.85-7.95 (2H, m)

MASS: 351 $(M+H)^+$

Preparation 20

To a stirred solution of $Pd(OAc)_2$ (75 mg, 0.34 mmol), $nBu_3P$ (136 mg, 0.67 mmol), and $Et_3N$ (442 mg, 4.37 mmol) in DMF (10 ml) was added 3-butene-1,2-diol (296 mg, 3.36 mmol) followed by methyl 3-bromophenylacetate (1.0 g, 4.37 mmol), and the reaction mixture was stirred at 100℃ for 5 h. The reaction mixture was poured into water (100 ml) and extracted with ethyl acetate. The organic layer was washed with brine, dried (magnesium sulfate) and evaporated in vacuo. The residue was purified by silica gel (25 g) column chromatography eluting with toluene/ethyl acetate (20:1) to give methyl 3-(4-hydroxy-3-oxobutyl)phenylacetate (193 mg, 24.4%) as an oil.

IR (neat): 3700-3100, 2950, 1732, 1261, 1159, 1069 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 2.73 (2H, t, J=7.5Hz), 2.96 (2H, t, J=7.5Hz), 3.06 (1H, t, J=4.8Hz), 3.60 (2H, s), 3.70 (3H, s), 4.19 (2H, d, J=4.8Hz), 7.05-7.35 (4H, m)

MASS: 237 $(M+H)^+$

Preparation 21

The following compounds were prepared by a similar procedure to that of Preparation 13.

(1) 1-(tert-Butyldimethylsilyloxy)-4-(4-methylphenyl)butan-2-ol was prepared as a colorless oil from the compound obtained in Preparation 18.

IR (neat): 3442, 2931, 2859, 1463, 1254, 1116 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 0.06 (6H, s), 0.90 (9H, s), 1.60-1.85 (2H, m), 2.32 (3H, s), 2.44 (1H, d, J=3.5Hz), 2.55-2.90 (2H, m), 3.30-3.80 (3H, m), 7.10 (4H, s)

MASS: 295 $(M+H)^+$

(2) 1-(tert-Butyldimethylsilyloxy)-4-[3-(ethoxycarbonyl)phenyl]-butan-2-ol was prepared as a colorless oil from the compound obtained in Preparation 19.

IR (neat): 3700-3100, 2933, 2860, 1718, 1279, 1110 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 0.07 (6H, s), 0.90 (9H, s), 1.40 (3H, t, J=7.1Hz), 1.65-1.85 (2H, m), 2.46 (1H, d, J=3.4Hz), 2.65-3.00 (2H, m), 3.35-3.75 (3H, m), 4.37 (2H, q, J=7.1Hz), 7.30-7.45 (2H, m), 7.80-7.95 (2H, m)

MASS: 353 $(M+H)^+$

(3) Methyl 3-[4-(tert-butyldimethylsilyloxy)-3-hydroxybutyl]-phenylacetate was prepared as a colorless oil from the compound obtained in Preparation 22.

IR (neat): 3800-3100, 2931, 2858, 1741, 1250, 1119 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 0.07 (6H, s), 0.90 (9H, s), 1.60-1.80 (2H, m), 2.45 (1H, d, J=3.6Hz), 2.55-2.95 (2H, m), 3.35-3.75 (8H, m), 7.05-7.35 (4H, m)

MASS: 353 $(M+H)^+$

Preparation 22

To an ice cooled solution of methyl 3-(4-hydroxy-3-oxobutyl)phenylacetate (472 mg, 2.00mmol) in DMF (10 ml) was added imidazole (264 mg, 3.88 mmol) followed by tert-butyldimethylsilyl chloride (408 mg, 5.99 mmol). After 30 minutes the ice-bath was removed and then the mixture was stirred overnight at room temperature. The reaction mixture was poured into water (100ml) and extracted with ethyl acetate. The organic layer was washed with brine, dried (magnesium sulfate), and concentrated in vacuo. The residue was purified by silica gel (20 g) column chromatography eluting with hexane/ethyl acetate (10:1) to give methyl 3-[4-(tert-butyldimethylsilyloxy)-3-oxobutyl]phenylacetate (664 mg, 94.9%) as a colorless oil.

IR (neat): 2952, 2933, 2856, 1738, 1250, 1153, 1101 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 0.07 (6H, s), 0.91 (9H, s), 2.75-3.00 (4H, m), 3.60 (2H, s), 3.69 (3H, s), 4.15 (2H, s), 7.05-7.30 (4H, m)

MASS: 351 $(M+H)^+$

Preparation 23

A solution of ethyl 2-(4-carbamoyl-1-imidazolyl)-4-phenylbutyrate (obtained in Preparation 2) in DMF (5 ml) was added to an ice-cooled solution of $POCl_3$ (0.71 ml) in DMF (6 ml) under nitrogen atmosphere. After 1.5 h, the solvent was poured into water (50 ml) and the solution was neutralized with saturated $NaHCO_3$aq. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel (16 g) column chromatography eluting with chloroform/methanol (100:1) to give ethyl 2-(4-cyano-1-imidazolyl)-4-phenylbutyrate (435mg,

101.2%).

IR (neat): 3132, 2978, 2933, 2235, 1741, 1236, 1157 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.28 (3H, t, J=7.1Hz), 2.20-2.80 (4H, m), 4.23 (2H, q, J=7.1Hz), 4.63 (1H, m), 7.00-7.40 (5H, m), 7.53 (1H, s), 7.58 (1H, s)

MASS: 284 $(M+H)^+$

Preparation 24

1-(tert-Butyldimethylsilyloxy)-3-phenoxypropan-2-ol was prepared from 3-phenoxy-1,2-propanediol and tert-butyldimethylsilyl chloride by a similar procedure to that of Preparation 22.

IR (neat): 3700-3100, 2931, 2860, 1244, 1092 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 0.08 (6H, s), 0.90 (9H, s), 2.54 (1H, d, J=5.4Hz), 3.75-4.15 (5H, m), 6.85-7.05 (3H, m), 7.25-7.35 (2H, m)

MASS: 283 $(M+H)^+$

Preparation 25

1-Naphthylmethylmagnesium chloride was prepared from magnesium turnings (2.88 g) and 1-(chloromethyl)naphthalene (6.98 g) in ether (80 ml) by the method of J. Am. Chem. Soc. (1943) 65, 295. A solution of lithium chloride (167 mg) and copper (II) chloride (266 mg) in THF (10 ml) was added dropwise to the ethereal solution of the Grignard reagent followed by addition of a solution of (2RS,3S)-3-(benzyloxy)-1,2-epoxybutane (3.52 g) in ether (30 ml) below -70℃. The mixture was stirred at -78℃ for 1 h, and then allowed to warm to room temperature and stirred overnight. After cooling, the mixture was quenched with saturated aqueous ammonium chloride solution (100 ml). The insoluble material was filtered through Celite and the filter cake was washed with ether. The filtrate and washings were combined, and the organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo to give an oil. Flash chromatography (hexane:ethyl acetate

= 9:1 → 4:1) gave (2S,3S)-2-benzyloxy-5-(1-naphthyl)pentan-3-ol (2.66 g, 42.0%) as the first eluate and (2S,3R)-2-benzyloxy-5-(1-naphthyl)pentan-3-ol (1.36 g, 21.5%) as the second eluate.

(2S,3S)-2-benzyloxy-5-(1-naphthyl)pentan-3-ol

IR (neat): 3558, 3458, 2870, 1078 $cm^{-1}$

NMR ($CDCl_3$, d): 1.17 (3H, d, J=6.0 Hz), 1.89 (2H, m), 2.70 (1H, d, J=4.0 Hz), 3.15 (1H, m), 3.30-3.60 (3H, m), 4.43 (1H, d, J=11.4 Hz), 4.67 (1H, d, J=11.4 Hz), 7.20-8.15 (12H, m)

$[\alpha]_D^{26}$ -27.8° (c 0.5, EtOH)

(2S,3R)-2-benzyloxy-5-(1-naphthyl)pentan-3-ol

IR (neat): 3556, 3458, 2871, 1088 $cm^{-1}$

NMR ($CDCl_3$, d): 1.16 (3H, d, J=6.3 Hz), 1.86 (2H, m), 2.19 (1H, d, J=4.0 Hz), 3.11 (1H, m), 3.32-3.55 (2H, m), 3.87 (1H, m), 4.47 (1H, d, J=11.8 Hz), 4.60 (1H, d, J=11.8 Hz), 7.19-8.06 (12H, m)

$[\alpha]_D^{26}$ +33.5° (c 0.5, EtOH)

Preparation 26

A solution of (S)-2-(benzyloxy)propanal (Bull. Chem. Soc. Jpn. (1989) 62, 3038, 16.25 g) in ether (200 ml) was added to a suspension of zinc bromide (26.75 g) in ether (50 ml) below 6℃ and then an ethereal solution of 2-(1-naphthyl)ethylmagnasium bromide, prepared from 2-(1-naphthyl)ethyl bromide (46.55 g) and magnesium turnings (9.63 g) in ether (300 ml), was added below 8℃. The mixture was stirred at 4℃ for 1 h and then THF (200 ml) was added. The final mixture was stirred overnight at room temperature. After cooling, the mixture was quenched with saturated aqueous ammonium chloride solution (200 ml) and insoluble material was filtered. The filtrate

was extracted with ethyl acetate and the extract was washed with brine, dried and concentrated in vacuo. Flash chromatography (hexane:ethyl acetate = 9:1) gave (2S,3S)-2-benzyloxy-5-(1-naphthyl)pentan-3-ol (9.78 g, 30.8%) as an oil.

Preparation 27

To an ice-cooled solution of (2S,3S)-2-benzyloxy-5-(1-naphthyl)pentan-3-ol (obtained in Preparation 26) (7.43 g) in dichloromethane (100 ml) was added methanesulfonyl chloride (2.15 ml) followed by triethylamine (3.88 ml). The mixture was stirred at 4 ℃ for 40 min. After being diluted with dichloromethane, the mixture was washed with water and brine, dried and concentrated in vacuo to give (2S,3S)-2-benzyloxy-5-(1-naphthyl)-3-pentyl methanesulfonate (9.92 g, 107.4%) as an oil. The product was used directly in the next step without further purification.

IR (neat): 1344, 1173 $cm^{-1}$

NMR ($CDCl_3$, d): 1.23 (3H, d, J=6.4Hz), 2.04-2.25 (2H, m), 2.98 (3H, s), 3.06-3.33 (2H, m), 3.82 (1H, m), 4.44 (1H, d, J=11.5Hz), 4.64 (1H, d, J=11.5Hz), 4.80 (1H, m), 7.25-8.02 (12H, m)

Preparation 28

The following compound was prepared by a similar procedure to that of Preparation 25.

(1) (2S,3S)-2-(benzyloxy)-5-[2-(trifluoromethyl)phenyl]pentan-3-ol was prepared from (S)-2-(benzyloxy)propanal.

NMR ($CDCl_3$, $\delta$): 1.19 (3H, d,J=6Hz), 1.6-1.9 (2H, m), 2.67 (1H,d,J=3Hz), 2.7-3.2 (2H,m), 3.3-3.6 (2H,m), 4.44 (1H,d,J=11Hz),4.67 (1H,d,J=11Hz), 7.2-7.7 (9H, m)

MASS: 361 $(M+Na)^+$

(2) (2S,3S)-2-(tert-butyldimethylsilyloxy)-5-phenyl-pentan-3-ol was prepared from (S)-2-(tert-butyldimethylsilyloxy)propanal (Synthesis 1996, 652, 3.00 g) and 2-phenylethyl bromide.

IR (neat): 3573,3473,2935,1078 $cm^{-1}$

NMR ($CDCl_3$, d): 0.09 (6H, s), 0.90 (9H, s), 1.13 (3H, d, J=6.2Hz), 1.66-1.77 (2H, m), 2.42 (1H, d, J=5.3Hz), 2.60-2.95 (2H, m), 3.30 (1H, m), 3.65 (1H, m), 7.14-7.32 (5H, m)

MS (ESI, m/z): 317$(M+Na)^+$

$[\alpha]_D^{27}$ -31.6° (c 0.5, EtOH)

(3) (2S,3S)-2-(tert-dimethylsilyloxy)-5-[2-(benzyloxy)phenyl]-pentan-3-ol was prepared from (S)-2-(tert-butyldimethyl-silyloxy)propanal.

NMR ($CDCl_3$, $\delta$): 0.05 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 1.08 (3H, d, J=6Hz), 1.6-1.9 (2H, m), 2.40 (1H, d, J=5Hz), 2.6-3.0 (2H, m), 3.2-3.4 (1H, m), 3.6-3.7 (1H, m), 5.09 (2H, s), 6.8-7.5 (9H, m)

MS: 423 $(M+Na)^+$

(4) (2S,3S)-2-(benzyloxy)-5-(2-naphthyl)pentan-3-ol was prepared from (S)-2-(benzyloxy)propanal.

IR (neat): 3442, 1078 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.18 (3H, d, J=6Hz), 1.7-2.0 (2H, m), 2.64 (1H, d, J=3Hz), 2.7-3.1 (2H, m), 3.3-3.6 (2H, m), 4.43 (1H, d, J=11Hz),4.67 (1H, d, J=11Hz), 7.2-7.6 (8H, m), 7.64 (1H, s), 7.6-7.9 (3H, m)

MS: 343 $(M+Na)^+$

(5) (2S,3S)-2-(benzyloxy)-6-(1-naphthyl)hexan-3-ol was prepared from (S)-2-(benzyloxy)propanal.

IR (neat): 3437, 1081 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.18 (3H, d, J=6Hz), 1.5-1.7 (2H, m), 1.7-

2.2 (2H, m), 2.59 (1H, d, J=4Hz), 3.0-3.2 (2H, m), 3.3-3.6 (2H, m), 4.41 (1H, d, J=11Hz), 4.66 (1H, d, J=11Hz), 7.2-7.6 (9H, m), 7.70 (1H, d, J=8Hz), 7.7-8.1 (2H, m)

MS: 357 $(M+Na)^+$

Preparation 29

The following compounds were prepared according to the procedure of Preparation 27.

(1) (2S,3R)-2-Benzyloxy-5-(1-naphthyl)-3-pentyl methanesulfonate was prepared from (2S,3R)-2-benzyloxy-5-(1-naphthyl)pentan-3-ol obtained in Preparation 25.

IR (neat): 1346, 1171 $cm^{-1}$

NMR ($CDCl_3$, d): 1.23 (3H, d, J=6.4Hz), 1.80-2.25 (2H, m), 3.08 (3H, s), 3.10 (1H, m), 3.40 (1H, m), 3.64 (1H, m), 4.58 (2H, s), 5.04 (1H, m), 7.30-8.05 (12H, m)

(2) (2S,3S)-2-(tert-Butyldimethylsilyloxy)-5-phenyl-3-pentyl methanesulfonate was prepared from (2S,3S)-2-(tert-butyldimethylsilyloxy)-5-phenyl-pentan-3-ol (obtained in Preparation 28(2)).

IR (neat): 2935, 1352, 1174 $cm^{-1}$

NMR ($CDCl_3$, d): 0.03 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.17 (3H, d, J=6.2Hz), 1.80-2.20 (2H, m), 2.60-2.90 (2H, m), 3.01 (3H, s), 4.10 (1H, m), 4.53 (1H, m), 7.10-7.40 (5H, m)

Example 1

$NaBH_4$ (491 mg) was added portionwise to an ice cooled solution of ethyl 2-(4-carbamoyl-1-imidazolyl)-4-phenylbutyrate (obtained in Preparation 2) (391 mg) in methanol (20 ml) under an nitrogen atmosphere. After the addition was completed, the reaction mixture

was stirred at room temperature for 30 minutes. Water was added, and the resulting mixture was stirred for several minutes and then evaporated under reduced pressure. The residue was partitioned between chloroform and water. The organic layer was washed with brine and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave 1-(1-hydroxy-4-phenyl-2-butyl)imidazole-4-carboxamide (347 mg) as a white solid.

mp: 127.0-129.5℃

IR (KBr): 3500-2700, 1664 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 2.06 (2H, q, J=7.6Hz), 2.39 (2H, t, J=7.6Hz), 3.63 (2H, t, J=5.5Hz), 4.10 (1H, qui, J=6.4Hz), 5.01 (1H, t, J=5.3Hz), 7.04 (1H, br s), 7.10-7.33 (6H, m), 7.70 (1H, s), 7.75 (1H, s)

MASS: 260 $(M+H)^+$

Example 2

The following compounds were obtained according to the similar manner to that of Example 1.

(1) 1-(2-Hydroxy-1-phenylethyl)imidazole-4-carboxamide was prepared from the compound obtained in Preparation 4(1).

mp: 147-149℃

IR (KBr): 3324, 3187, 1668 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 4.26 (2H, d, J=5.4Hz), 5.35 (2H, br), 7.05 (1H, br), 7.10-7.50 (5H, m), 7.64 (1H, s), 7.75 (1H, s)

MASS: 232 $(M+H)^+$

(2) 1-(1-Hydroxy-2-octyl)imidazole-4-carboxamide was prepared from the compound obtained in Preparation 4(2).

mp: 97.5-100.5℃

IR (KBr): 3324, 3178, 2927, 2857, 1662 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 0.83 (3H, t, J=6.5Hz), 0.90-1.35 (8H, m), 1.60-1.80 (2H, m), 3.60 (2H, t, J=5.6Hz), 4.09 (1H, qui, J=6.5Hz), 4.98 (1H, t, J=5.3Hz), 7.00 (1H, s), 7.22 (1H, s), 7.67 (2H, s)

MASS: 240 $(M+H)^+$

(3) 1-(1-Hydroxy-2-pentyl)imidazole-4-carboxamide was prepared from the compound obtained in Preparation 5.

mp: 160℃

IR (KBr): 3336, 3172, 1654 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 0.84 (3H, t, J=7.2Hz), 1.10 (2H, m), 1.70 (2H, q, J=7.5Hz), 3.61 (2H, t, J=5.4Hz), 4.12 (1H, qui, J=6.5Hz), 4.99 (1H, t, J=5.4Hz), 7.01 (1H, s), 7.24 (1H, s), 7.69 (2H, s)

MASS: 198 $(M+H)^+$

(4) 1-(1,4-Dihydroxy-2-butyl)imidazole-4-carboxamide was prepared from the compound obtained in Preparation 6.

IR (KBr): 3700-3100, 1670 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 1.86 (2H, m), 3.10-3.45 (2H, m), 3.62 (2H, t, J=5.5Hz), 4.29 (1H, m), 4.60 (1H, t, J=5.0Hz), 5.01 (1H, t, J=5.3Hz), 7.02 (1H, s), 7.25 (1H, s), 7.65 (1H, s), 7.68 (1H, s)

MASS: 200 $(M+H)^+$

(5) 1-[1-hydroxy-4-(1-naphthyl)-2-butyl]imidazole-4-carboxamide was prepared from the compound obtained in Preparation

17(1).

mp: 138-140℃

IR (KBr): 3600-2800, 1660, 1598 $cm^{-1}$ $(M+H)^+$

NMR (DMSO-$d_6$, $\delta$) : 2.17 (2H, t, J=7.7Hz), 2.70-3.10 (2H, m), 3.68 (2H, t, J=5.4Hz), 4.27 (1H, m), 5.04 (1H, t, J=5.3Hz), 7.06 (1H, brs), 7.20-7.60 (5H, m), 7.75-8.00 (5H, m)

MASS: 310 $(M+H)^+$

(6) 1-[1-Hydroxy-4-(3-methylphenyl)-2-butyl]imidazole-4-carboxamide was obtained as a white solid from the compound obtained in Preparation 17(2).

mp: 115.5-117.5℃

IR (KBr): 3325, 3195, 3110, 2935, 2854, 1662, 1604 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 1.90-2.50 (7H, m), 3.62 (2H, m), 4.10 (1H, m), 5.01 (1H, br), 6.85-7.40 (6H, m), 7.70 (1H, s), 7.74 (1H, s)

MASS: 274 $(M+H)^+$

(7) 1-{1-Hydroxy-4-[3-(trifluoromethyl)phenyl]-2-butyl}-imidazole-4-carboxamide was obtained as a white solid from the compound obtained in Preparation 17(3).

mp: 103-106℃

IR (KBr): 3332, 3195, 3143, 1670, 1335 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 2.11 (2H, q, J=8.0Hz), 2.35-2.75 (2H, m), 3.64 (2H, m), 4.13 (1H, m), 5.03 (1H, br s), 7.03 (1H, br s), 7.26 (1H, br s), 7.40-7.65 (4H, m), 7.71 (1H, s), 7.77 (1H, s)

MASS: 328 $(M+H)^+$

(8) 1-[1-Hydroxy-4-(3-hydroxyphenyl)-2-butyl]imidazole-4-carboxamide was obtained from the compound obtaind in Preparation

17(4).

IR (KBr): 3700-2800, 1658, 1600 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 1.90-2.50 (4H, m), 3.62 (2H, m), 4.14 (1H, m), 5.09 (1H, t, J=5.3Hz), 6.45-6.65 (3H, m), 6.95-7.60 (4H, m), 7.74 (1H, s), 7.80 (1H, s), 9.37 (1H, s)

MASS: 276 $(M+H)^+$

Example 3

The following compounds were obtained according to a similar manner to that of Preparation 2.

(1) 1-[(2S)-2-(Benzyloxy)-5-phenyl-3-pentyl]imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 10.

IR (neat): 3700-2800, 1673, 1658 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 0.98-1.08 (3H, m), 2.10-2.75 (4H, m), 3.60-4.00 (2H, m), 4.05-4.70 (2H, m), 5.39 (1H, brs), 6.90-7. 10 (3H, m), 7.15-7.45 (9H, m), 7.67 (1H, dd, J=6.1, 1.3Hz)

MASS: 364 $(M+H)^+$, 386 $(M+Na)^+$

(2) 1-[(2S)-2-(Benzyloxy)-6-phenyl-3-hexyl]imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 11(1).

IR (neat): 3500-2800, 1666, 1589, 1236, 1095 $cm^{-1}$

NMR ($CDCl_3$, $\delta$) : 0.98-1.08 (3H, m), 1.30-2.20 (4H, m), 2.30-3.20 (2H, m), 3.50-4.10 (2H, m), 4.20-4.65 (2H, m), 5.37(1H, br s), 6.95(1H, brs), 7.00-7.80 (12H, m)

MASS: 378 $(M+H)^+$

(3) 1-[(2S)-2-(Benzyloxy)-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 11(2).

IR (neat): 3700-2800, 1666, 1594, 1236, 1097 $cm^{-1}$

NMR ($CDCl_3$, $\delta$ ): 1.04 (3H, d, J=6.2Hz), 2.10-2.60 (2H, m), 2.70-3.15 (2H, m), 3.50-4.10 (2H, m), 4.20-4.65 (2H, m), 5.41 (1H, brs), 7.01 (1H, brs), 7.10-7.60 (9H, m), 7.65-7.95 (5H, m)

MASS: 414 $(M+H)^+$

(4) 1-[1-(tert-Butyldimethylsilyloxy)-4-(4-methylphenyl)-2-butyl]imidazole-4-carboxamide was prepared from the compound obtained Preparation 1 and the compound obtained in Preparation 21(1).

NMR ($CDCl_3$, $\delta$): -0.07 (3H, s), -0.05 (3H, s), 0.84 (9H, s), 1.95-2.25 (2H, m), 2.32 (3H, s), 2.35-2.80 (2H, m), 3.65-4.10 (3H, m), 5.40 (1H, br s), 6.90-7.15 (5H, m), 7.44 (1H, s), 7.64 (1H, s)

MASS: 388 $(M+H)^+$

(5) 1-{1-(tert-Butyldimethylsilyloxy)-4-[3-(ethoxycarbonyl)-phenyl]-2-butyl}imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 21(2).

IR (neat): 3700-3050, 2931, 2860, 1716, 1666, 1595, 1240, 1095 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): -0.06 (3H, s), -0.04 (3H, s), 0.83 (9H, s), 1.41 (3H, t, J=7.1Hz), 2.18 (2H, m), 2.40-2.80 (2H, m), 3.60-4.10 (3H, m), 3.65-4.10 (3H, m), 4.39 (2H, q, J=7.1Hz), 5.37 (1H, br s), 6.95 (1H, br s), 7.20-7.42 (2H, m), 7.45 (1H, s), 7.65 (1H, s), 7.75-7.95 (2H, m)

MASS: 446 $(M+H)^+$

(6) 1-{1-(tert-Butyldimethylsilyloxy)-4-{3-[(methoxycarbonyl)-methyl]phenyl}-2-butyl}imidazole-4-carboxamide was prepared from

the compound obtained in Preparation 1 and the compound obtained in Preparation 21(3).

IR (neat): 3800-3000, 2952, 2858, 1739, 1676, 1257, 1126 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): -0.07 (3H, s), -0.04 (3H, s), 0.83 (9H, s), 2.05-2.25 (2H, m), 2.30-2.75 (2H, m), 3.60 (2H, s), 3.70-3.85 (5H, m), 3.98 (1H, m), 5.39 (1H, br s), 6.90-7.35 (5H, m), 7.46 (1H, s), 7.65 (1H, s)

MASS: 446 $(M+H)^+$

(7) 1-(1-Hydroxy-3-phenoxy-2-propyl)imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 24.

mp: 147.5-149.5℃

IR (KBr): 3330, 3188, 1662, 1600, 1246 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 3.80-4.30 (5H, m), 5.53 (1H, d, J=4.1Hz), 6.85-7.10 (4H, m), 7.20-7.40 (3H, m), 7.63 (2H, s)

MASS: 262 $(M+H)^+$

(8) 1-[(2S,3R)-2-(benzyloxy)-5-(2-methylphenyl)-3-pentyl]-imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 11(3).

NMR ($CDCl_3$, $\delta$): 1.07 (3H,d,J=6Hz), 2.0-2.6 (4H,m), 2.18 (3H,s), 3.6-3.8 (1H,m), 3.9-4.1 (1H,m), 4.38 (1H,d,J=11Hz), 4.58 (1H,d,J=11Hz), 5.39 (1H,s), 6.9-7.4 (10H,m), 7.45 (1H,d,J=1Hz), 7.67 (1H,d,J=1Hz)

MASS: 378 $(M+H)^+$

(9) 1-[(2S,3R)-2-(benzyloxy)-5-(2-chlorophenyl)-3-pentyl]-imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 11(4).

NMR ($CDCl_3$, $\delta$): 1.08 (3H,d,J=6Hz), 2.0-2.5 (2H,m), 2.5-2.7 (2H,m), 3.6-3.7 (1H,m), 3.9-4.1 (1H,m), 4.38

(1H,d,J=12Hz), 4.58 (1H,d,J=12Hz), 5.37 (1H,s), 6.9-7.4 (10H,m), 7.48 (1H,d,J=1Hz), 7.67 (1H,d,J=1Hz)

MASS: 420 $(M+Na)^+$

(10) 1-[(2S,3R)-2-(benzyloxy)-5-(2-methoxyphenyl)-3-pentyl]-imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 11(5).

NMR ($CDCl_3$, $\delta$): 1.04 (3H,d,J=6Hz), 2.0-2.6 (4H,m), 3.6-3.7 (1H,m), 3.80 (3H,s), 3.9-4.1 (1H,m), 4.39 (1H,d,J=12Hz), 4.57 (1H,d,J=12Hz), 5.38 (1H,s), 6.8-7.4 (10H,m), 7.45 (1H,d,J=1Hz), 7.69 (1H,d,J=1Hz)

MASS: 394 $(M+H)^+$

(11) 1-[(2S,3R)-2-(benzyloxy)-5-(2-hexyloxyphenyl)-3-pentyl]-imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 11(6).

NMR ($CDCl_3$, $\delta$): 0.8-1.0 (3H,m), 1.05 (3H,d,J=6Hz), 1.2-1.5 (6H,m), 1.6-1.9 (2H,m), 2.0-2.6 (4H,m), 3.6-3.7 (1H,m), 3.8-4.0 (3H,m), 4.38 (1H,d,J=12Hz), 4.56 (1H,d,J=12Hz), 5.37 (1H,s), 6.8-7.4 (10H,m), 7.44 (1H,s), 7.67 (1H,s)

MASS: 464 $(M+H)^+$

(12) 1-[(2S,3R)-2-(benzyloxy)-5-(2,3-dichlorophenyl)-3-pentyl]-imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 11(7).

NMR ($CDCl_3$, $\delta$): 1.08 (3H,d,J=6Hz), 2.0-2.5 (2H,m), 2.5-2.7 (2H,m), 3.6-4.1 (2H,m), 4.38 (1H,d,J=12Hz), 4.59 (1H,d,J=12Hz), 5.45 (1H,s), 6.9-7.4 (9H,m), 7.48 (1H,d,J=1Hz), 7.67 (1H,d,J=1Hz)

MASS: 432 $(M+H)^+$

(13) 1-[(2S,3R)-2-(benzyloxy)-5-(2-phenethyloxyphenyl)-3-

pentyl]imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 11(8).

NMR ($CDCl_3$, $\delta$): 0.99 (3H,d,J=6Hz), 1.9-2.6 (4H,m), 3.06 (2H,t,J=7Hz), 3.5-3.6 (1H,m), 3.8-4.6 (5H,m), 5.34 (1H,s), 6.7-7.0 (3H,m), 7.1-7.4 (13H,m), 7.62 (1H,d,J=1Hz)

MASS: 484 $(M+H)^+$

(14) 1-[(2S,3R)-2-(benzyloxy)-5-(2,3-dimethylphenyl)-3-pentyl]-imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 11(9).

NMR ($CDCl_3$, $\delta$): 1.06 (3H,d,J=6Hz), 2.0-2.6 (4H,m), 2.09 (3H,s), 2.26 (3H,s), 3.6-3.7 (1H,m), 3.9-4.0 (1H,m), 4.38 (1H,d,J=12Hz), 4.58 (1H,d,J=12Hz), 5.39 (1H,s), 6.7-7.4 (9H,m), 7.46 (1H,d,J=1Hz), 7.67 (1H,d,J=1Hz)

MASS: 392 $(M+H)^+$

(15) 1-{(2S,3R)-2-(benzyloxy)-5-[2-(trifluoromethyl)phenyl]-3-pentyl}imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 28(1).

NMR ($CDCl_3$, $\delta$): 1.09 (3H,d,J=6Hz), 2.0-2.8 (4H,m), 3.6-3.8 (1H,m), 3.9-4.1 (1H,m), 4.39 (1H,d,J=12Hz), 4.59 (1H,d,J=12Hz), 5.40 (1H,s), 6.9-7.7 (12H,m)

MASS: 432 $(M+H)^+$

(16) 1-{(2S,3R)-2-(benzyloxy)-5-[2,3-(methylenedioxy)phenyl]-3-pentyl}imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 11(10).

NMR ($CDCl_3$, $\delta$): 1.06 (3H, d, J=6Hz), 2.0-2.6 (4H, m), 3.6-4.0 (2H, m), 4.38 (1H, d, J=12Hz), 4.58 (1H, d, J=12Hz),

5.38 (1H, s), 5.90 (2H, s), 6.4-6.8 (3H, m), 6.96 (1H, s), 7.2-7.4 (5H, m), 7.43 (1H, d, J=1Hz), 7.65 (1H, d, J=1Hz)

MS: 408 $(M+H)^+$

(17) 1-[(2S,3R)-2-(tert-butyldimethylsilyloxy)-5-(2-benzyloxyphenyl)-3-pentyl]imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 28(3).

NMR ($CDCl_3$, $\delta$): -0.07 (3H, s), -0.02 (3H, s), 0.84 (9H, s), 0.93 (3H, d, J=6Hz), 1.8-2.8 (4H, m), 3.7-3.9 (2H, m), 5.07 (2H, s), 5.35 (1H, s), 6.8-7.4 (11H, m), 7.61 (1H, s)

MS: 494 $(M+H)^+$

(18) 1-[(2S,3R)-2-(benzyloxy)-5-(2-naphthyl)-3-pentyl]imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 28(4).

IR (neat): 1662 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.06 (3H, d, J=6Hz), 2.1-2.9 (4H, m), 3.6-3.8 (1H, m), 3.8-4.1 (1H, m), 4.37 (1H, d, J=12Hz), 4.57 (1H, d, J=12Hz), 5.45 (1H, s), 7.0 (1H, s), 7.2-7.8 (14H, m)

MS: 414 $(M+H)^+$

(19) 1-[(2S,3R)-2-(benzyloxy)-6-(1-naphthyl)-3-hexyl]imidazole-4-carboxamide was prepared from the compound obtained in Preparation 1 and the compound obtained in Preparation 28(5).

IR (neat): 1658 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.04 (3H, d, J=6Hz), 1.5-2.3 (4H, m), 2.9-3.2 (2H, m), 3.5-3.7 (1H, m), 3.8-4.1 (1H, m), 4.37 (1H, d, J=12Hz), 4.57 (1H, d, J=12Hz), 5.51 (1H, s), 6.97 (1H, s) 7.1-8.0 (14H, m)

MS: 428 $(M+H)^+$

(20) Methyl 1-[(2S,3R)-2-benzyloxy-5-(1-naphthyl)-3-pentyl]-imidazole-4-carboxylate was prepared from (2S,3S)-2-benzyloxy-5-(1-naphthyl)pentan-3-ol (obtained in Preparation 26) and methyl imidazole-4-carboxylate.

IR (neat): 2945, 1726, 1672 $cm^{-1}$

NMR ($CDCl_3$, d): 1.06 (3H, d, J=6.2Hz), 2.15-2.60 (2H, m), 2.75-3.10 (2H, m), 3.65 (1H, m), 3.91 (3H, s), 3.96 (1H, m), 4.33 (1H, d, J=11.5Hz), 4.55 (1H, d, J=11.5Hz), 7.10-7.90 (14H, m)

MASS (APCI, m/z): 429 $(M+H)^+$

$[\alpha]_D^{27}$ +13.7° (c 0.65, EtOH)

Example 4

Twenty percent palladium hydroxide on carbon (30 mg) was added to a stirred solution of 1-[(2S)-2-benzyloxy-5-phenyl-3-pentyl]imidazole-4-carboxamide (obtained in Example 3(1))(107 mg) in cyclohexene (5 ml) and ethanol (12.5 ml). The resulting mixture was stirred at reflux temperature for 12 hours. After cooling to room temperature, the mixture was filtered through Celite, and the insoluble material on the filter was washed with ethanol. The filtrate and washing were combined and then concentrated in vacuo. The resulting residue was purified by silica gel (3 g) chromatography eluted with chloroform/methanol (50:1) to give 1-[(2S)-2-hydroxy-5-phenyl-3-pentyl]imidazole-4-carboxamide (69.1 mg).

IR (KBr): 3338, 2969, 1658 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 0.84-0.93 (3H, m), 2.00-2.50 (4H, m), 3.70-4.00 (2H, m), 4.95-5.10 (1H, m), 6.95-7.40 (7H, m), 7.66 (1H, d, J=2.2Hz), 7.72 (1H, d, J=4.1Hz)

MASS: 274 $(M+H)^+$

Example 5

The following compounds were obtained according to a similar manner to that of Example 4.

(1) 1-[(2S)-2-hydroxy-6-phenyl-3-hexyl]imidazole-4-carboxamide was prepared from the compound obtained in Example 3(2).

IR (KBr): 3700-2800, 1660, 1594 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 0.80-1.00 (3H, m), 1.15-1.55 (2H, m), 1.60-2.05 (2H, m), 2.40-2.70 (2H, m), 3.70-4.10 (2H, m), 4.95-5.10 (1H, m), 6.90-7.35 (7H, m), 7.60-7.75 (2H, m)

MASS: 288 $(M+H)^+$

(2) (2S)-2-hydroxy-5-(1-naphthyl)-3-pentylimidazole-4-carboxamide was prepared from the compound obtained in Example 3(3).

mp: 95-98℃

IR (KBr): 3336, 1658, 1594 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 0.80-1.00 (3H, m), 2.05-2.45 (2H, m), 2.60-3.15 (2H, m), 3.70-4.20 (2H, m), 5.05-5.15 (1H, m), 7.07 (1H, brs), 7.20-7.60 (5H, m), 7.70-8.00 (5H, m)

MASS: 324 $(M+H)^+$

Example 6

Triethylamine (1.06 g) was added dropwise to a stirred mixture of (R)-1-(tert-butyldimethylsilyl-oxy)-4-phenylbutan-2-ol (obtained in Preparation 14) (2.10 g) and methanesulfonyl chloride (1.20 g) in dichloromethane (20 ml) at ice-bath temperature. After 1 hour, the reaction mixture was partitioned between dichloromethane and water. The organic layer was washed with brine and dried over $MgSO_4$, and concentrated in vacuo to give the methanesulfonate (2.74 g) as an oil. This material was used for the next reaction without further purification.

NaH (60% in mineral oil, 299 mg) was added to a solution of methyl 4-imidazolecarboxylate (942 mg) in DMF (20 ml) at room

temperature. The reaction mixture was stirred for 30 minutes. The methanesulfonate prepared above was added and the resulting mixture was stirred for 37 hours at 70℃.

The reaction mixture was cooled to 10℃ in an ice bath, and the insoluble material was filtered and washed thoroughly with dichloromethane. The filtrate and the washing were combined and then washed with brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel (50 g) column chromatography eluting with toluene/ethyl acetate (20:1) to give methyl (S)-1-[1-(tert-butyldimethylsilyloxy)-4-phenyl-2-butyl]imidazole-4-carboxylate (1.52g).

IR (neat): 2950, 2933, 2857, 1725, 1675, 1189, 1122 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): -0.06 (3H, s), -0.05 (3H, s), 0.84 (9H, s), 2.10-2.25 (2H, m), 2.35-2.75 (2H, m), 3.70-3.80 (2H, m), 3.91 (3H, s), 4.00 (1H, m), 7.05-7.38 (5H, m), 7.51 (1H, s), 7.69 (1H, s)

MASS: 3S9 $(M+H)^+$

Example 7

A solution of 28% NaOMe in methanol (772 mg) was added to an ice cooled solution of aminoguanidine hydrochloride (332 mg) in methanol (5 ml). After 10 minutes, methyl (S)-1-[1-(tert-butyldimethylsilyloxy)-4-phenyl-2-butyl]-imidazole-4-carboxylate (obtained in Example 6) (389 mg) in methanol (2 ml) was added to the mixture and the resulting mixture was stirred at reflux for 22 hours. After cooling, the insoluble material was removed and then the filtrate was evaporated. The residue was diluted with water and the solution was acidified to pH 4 with 6N HClaq. The resulting mixture was washed with $CHCl_3$. The aqueous layer was purified by HP-20 (50 cc) column chromatography eluting with water/2-propanol (9:1) and lyophilized to give (S)-2-[4-(5-amino-1,2,4-triazol-3-yl)-1-imidazolyl]-4-phenylbutan-1-ol (107 mg).

mp: 80℃ (decompose)

IR (KBr): 3700-2700, 1641, 1602, 1238, 1058 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.95-2.60 (4H, m), 3.64 (2H, brs), 4.10 (1H, m), 5.02 (1H, brs), 5.40 (2H, br), 7.10-7.35 (6H, m), 7.55 (1H, s), 7.70 (1H, s)

MASS: 299 $(M+H)^+$

Example 8

A solution of 28% NaOMe in methanol (583 mg) was added to an ice cooled solution of guanidine hydrochloride (307 mg) in DMF (5 ml). After 10 minutes, methyl (S)-1-[1-(tert-butyl-dimethylsilyloxy)-4-phenyl-2-butyl]imidazole-4-carboxylate (obtained in Example 6) (250 mg) in DMF (2 ml) was added to the mixture and the resulting mixture was stirred at 100℃ for 5 hours. After cooling, the reaction mixture was poured into water (30 ml) and the solution was washed with ethyl acetate. The aqueous layer was purified by HP-20 (40 cc) column chromatography eluting with water/2-propanol (9:1) and lyophilized to give (S)-1-[1-hydroxy-4-phenyl-2-butyl]imidazole-4-carbonylguanidine (55.4 mg)

mp: 111-113℃

IR (KBr): 3700-2700, 1639, 1592, 1517, 1405 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) 1.90-2.60 (4H, m), 3.62 (2H, d, J=5.0), 4.07 (1H, m), 5.02 (1H, brs), 7.00-8.00 (11H, m)

MASS: 302 $(M+H)^+$

Example 9

To an ice cooled solution of 1-[1-(tert-butyldimethylsilyloxy)-4-(4-methylphenyl)-2-butyl]imidazole-4-carboxamide (obtained in Example 3(4))(194 mg, 0.50 mmol) in THF (5 ml) was added dropwise 1.0M $Bu_4NF$ in THF (1.0 ml). After the addition was completed, the reaction mixture was stirred at ice-bath temperature for 1h. 25% $AcONH_4$ (4 ml) was added, and the resulting

mixture was stirred for several minutes and then extracted with chloroform. The organic layer was washed with brine, dried (sodium sulfate) and concentrated in vacuo. The residue was purified by silica gel (5g) column chromatography eluting with chloroform/methabol (20:1) to give 1-[1-hydroxy-4-(4-methylphenyl)-2-butyl]imidazole-4-carboxamide (44.9mg, 32.9%) as a white solid.

mp: 138-141℃

IR (KBr): 3320, 3193, 2852, 1693, 1668, 1606 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 1.90-2.15 (2H, m), 2.20-2.50 (5H, m), 3.61 (2H, t, J=5.4Hz), 4.08 (1H, m), 5.00 (1H, t, J=5.3Hz), 6.90-7.15 (5H, m), 7.27 (1H, br s), 7.69 (1H, s), 7.74 (1H, s)

MASS: 274 $(M+H)^+$

Example 10

The following compound was prepared by a similar procedure to that of Example 9.

(1) 1-{1-Hydroxy-4-[3-(ethoxycarbonyl)phenyl]-2-butyl}-imidazole-4-carboxamide was prepared from the compound obtained in Example 3(5).

mp: 92-95℃

IR (KBr): 3322, 3193, 2954, 1720, 1662, 1604, 1278 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 1.32 (3H, t, J=7.1Hz), 2.00-2.20 (2H, m), 2.35-2.55 (2H, m), 3.64 (2H, br), 4.31 (2H, q, J=7.1Hz), 5.03 (1H, br s), 7.03 (1H, br s), 7.26 (1H, br s), 7.40-7.50 (2H, m), 7.65-7.85 (4H, m)

MASS: 332 $(M+H)^+$

(2) 1-{1-Hydroxy-4-[3-(methoxycarbonylmethyl)phenyl]-2-butyl}imidazole-4-carboxamide was prepared from the compound

obtained in Example 3(6).

mp: 138.5-141.0℃

IR (KBr): 3600-3000, 2951, 1738, 1651, 1583, 1267 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 1.90-2.20 (2H, m), 2.20-2.50 (2H, m), 3.50-3.75 (7H, m), 4.10 (1H, m), 5.01 (1H, t, J=5.3Hz), 6.90-7.35 (6H, m), 7.70 (1H, s), 7.75 (1H, s)

MASS: 332 $(M+H)^+$

(3) 1-[(2S,3R)-2-hydroxy-5-(2-benzyloxyphenyl)-3-pentyl]-imidazole-4-carboxamide was prepared from the compound obtained in Example 3 (17).

NMR ($CDCl_3$, $\delta$): 1.02 (3H, d, J=6Hz), 1.9-2.8 (5H, m), 3.8-4.0 (2H, m), 5.07 (2H, s), 5.38 (1H, s), 6.8-7.4 (11H, m), 7.66 (1H, d, J=1Hz)

MS: 380 $(M+H)^+$

$[\alpha]_D^{27}$ = +16.2° (c 1.0, EtOH)

Example 11

Sodium methoxide (39 mg, 0.72 mmol) was added to a stirred solution of 1-{1-hydroxy-4-[3-(ethoxycarbonyl)phenyl]-2-butyl}-imidazole-4-carboxamide (obtained in Example 10(1))(60 mg, 0.18 mmol) in formamide (1.5ml), and the reaction mixture was stirred at 110℃ for 3 h. After cooling, the reaction mixture was poured into water (5 ml). The residue was purified by HP-20 (16 cc) column chromatography eluting with water/2-propanol (9:1) and lyophilized to give 1-[4-(3-carbamoylphenyl)-1-hydroxy-2-butyl]imidazole-4-carboxamide (39.2 mg, 71.6%) as an amorphous solid.

IR (KBr): 3700-2800, 1660, 1592, 1402 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 2.09 (2H, m), 2.30-2.65 (2H, m), 3.64 (2H, t, J=5.4Hz), 4.14 (1H, m), 5.04 (1H, t, J=5.3Hz), 7.05 (1H, br s), 7.20-7.50 (4H, m), 7.65-7.85 (4H, m), 7.93 (1H, br

s)

MASS: 332 $(M+H)^+$

Example 12

The following compound was prepared by a similar procedure to that of Example 1.

(1) 1-{1-hydroxy-4-[3-(2-hydroxyethyl)phenyl]-2-butyl}-imidazole-4-carboxamide was prepared from the compound obtained in Example 10(2).

IR (KBr): 3700-3000, 2927, 2861, 1658, 1595, 1414, 1055 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 1.90-2.20 (2H, m), 2.20-2.50 (2H, m), 2.68 (2H, t, J=7.1Hz), 3.50-3.70 (4H, m), 4.10 (1H, m), 4.61 (1H, t, J=5.2Hz), 5.01 (1H, t, J=5.4Hz), 6.90-7.35 (6H, m), 7.70 (1H, s), 7.74 (1H, s)

MASS: 304 $(M+H)^+$

(2) 1-[1-Hydroxy-4-phenyl-2-butyl]imidazole-4-carbonitrile was prepared from the compound obtained in Preparation 23.

mp: 111-115℃

IR (KBr): 3500-3000, 2943, 2867, 2237, 1078 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 1.95-2.60 (4H, m), 3.55-3.70 (2H, m), 4.18 (1H, m), 5.06 (1H, t, J=5.4Hz), 7.05-7.35 (5H, m), 7.93 (1H, s), 8.25 (1H, s)

MASS: 242 $(M+H)^+$

Example 13

A mixture of methyl (S)-1-[1-(tert-butyldimethylsilyloxy)-4-phenyl-2-butyl]imidazole-4-carboxylate (obtained in Example 6) (300 mg, 0.77 mmol) and hydrazine monohydrate (5 ml) in DMF (3 ml) was stirred at 100℃ for 2 h.

After cooling, the reaction mixture was poured into water (10ml)

and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by silica gel (10 g) column chromatography eluting with chloroform/methanol (100:1) to give (S)-1-[1-(tert-butyldimethylsilyloxy)-4-phenyl-2-butyl]imidazole-4-carbohydrazide (274 mg, 91.5%).

IR (neat): 3700-3000, 2933, 2858, 1646, 1568, 1466, 1252, 1120 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): -0.07 (3H, s), -0.05 (3H, s), 0.83 (9H, s), 2.05-2.75 (4H, m), 3.65-4.10 (5H, m), 7.00-7.40 (5H, m), 7.43 (1H, s), 7.63 (1H, s)

MASS: 389 $(M+H)^+$

Example 14

A powder of NaOMe (417mg, 7.72mmol) was added to an ice cooled solution of hydroxylamine hydrochloride (536 mg, 7.72 mmol) in methanol (5 ml). After 30 minutes, methyl (S)-1-[1-(tert-butyldimethylsilyloxy)-4-phenyl-2-butyl]imidazole-4-carboxylate (obtained in Example 6)(389 mg, 1.0 mmol) in methanol (2 ml) was added to the mixture and the resulting mixture was stirred at reflux for 3 day. After cooling, the insoluble material was removed and then the filtrate was evaporated. The residue was diluted with water and the solution was acidified to pH 4 with 1N HClaq. The resulting mixture was washed with $CHCl_3$. The aqueous layer was purified by HP-20 (40 cc) column chromatography eluting with water/2-propanol (9:1) and lyophilized to give (S)-1-[1-hydroxy-4-phenyl-2-butyl]-imidazole-4-carbohydroxamic acid (92.5 mg, 43.5%) as an amorphous solid.

IR (neat): 3700-2700, 1645, 1566, 1238, 1141 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 1.90-2.60 (4H, m), 3.63 (2H, m), 4.10 (1H, m), 5.01 (1H, br), 7.05-7.40 (5H, m), 7.70 (1H, s), 7.76 (1H, s), 8.72 (1H, br), 10.62 (1H, br s)

MASS: 276 $(M+H)^+$

Example 15

A powder of NaOMe (67.2 mg, 1.24 mmol) was added to a solution of hydroxylamine hydrochloride (86.4 mg, 1.24 mmol) in methanol (2 ml) at room temperature. After 30 minutes, 1-(1-hydroxy-4-phenyl-2-butyl)imidazole-4-carbonitrile (obtained in Example 12(2))(100 mg, 0.41 mmol) was added to the mixture and the resulting mixture was stirred at reflux for 2 h. After cooling, the insoluble material was removed and then the filtrate was evaporated. The residue was purified by silica gel (5 g) column chromatography eluting with chloroform/methanol (20:1) and concentrated in vacuo. The residue was triturated with isopropyl ether to give N-hydroxy-1-[1-hydroxy-4-phenyl-2-butyl]imidazole-4-carboximidamide (86.3 mg, 76.0%) as an amorphous solid.

IR (KBr): 3700-2800, 1649, 1604, 1496 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 1.90-2.60 (4H, m), 3.62 (2H, t, J=4.9Hz), 4.09 (1H, m), 5.04 (1H, t, J=5.2Hz), 6.06 (2H, br s), 7.10-7.40 (5H, m), 7.58 (1H, s), 7.75 (1H, s), 9.41 (1H, br s)

MASS: 275 $(M+H)^+$

Example 16

A mixture of 1-(1-hydroxy-4-phenyl-2-butyl)imidazole-4-carbonitrile (obtained in Example 12(2))(100 mg, 0.41 mmol), ammonium chloride (111 mg, 2.07 mmol) and sodium azide (135 mg, 2.07 mmol) in DMF (4 ml) was stirred at 100℃ for 8 h.

After cooling, the reaction mixture was poured into water (30 ml) and the solution was washed with $CHCl_3$. The aqueous layer was purified by HP-20 (16 cc) column chromatography eluting with water/2-propanol (9:1) and lyophilized to give 1-(1-hydroxy-4-phenyl-2-butyl)-4-(5-tetrazolyl)imidazole (63.3 mg, 53.8%) as an

amorphous solid.

IR (KBr): 3700-2700, 1651, 1612, 1496, 1458, 1250 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$): 1.95-2.60 (4H, m), 3.66 (2H, m), 4.09 (1H, m), 5.03 (1H, br), 7.05-7.35 (5H, m), 7.55 (1H, s), 7.68 (1H, s), 9.41 (1H, br s)

MASS: 285 $(M+H)^+$

Example 17

A suspension of imidazole-4-carboxamide (obtained in Preparation 1)(207 mg) in DMF (3 ml) was treated with sodium hydride (60% in mineral oil, 87 mg) at ice-bath temperature and the mixture was stirred at room temperature for 20 min. A solution of (2S,3S)-2-benzyloxy-5-(1-nephthyl)-3-pentyl methanesulfonate (obtained in Preparation 27)(0.62 mg) in DMF (5 ml) was added and the mixture was stirred at 80 ℃ for 48 h. After cooling, the mixture was filtered to remove the insoluble material. The filtrate was poured into water and extracted with ethyl acetate. The extract was washed with water and brine, dried and concentrated in vacuo. Flash chromatography (dichloromethane:methanol = 50:1) gave 1-[(2S,3R)-2-benzyloxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxamide (221 mg, 34.4%) as an oil.

IR (neat): 3458, 3332, 3184, 1666, 1593 $cm^{-1}$

NMR ($CDCl_3$, d): 1.04 (3H, d, J=6.3Hz), 2.15-2.60 (2H, m), 2.80-3.10 (2H, m), 3.64 (1H, m), 3.98 (1H, m), 4.53 (1H, d, J=11.6Hz), 4.55 (1H, d, J=11.6Hz), 5.49 (1H, bs), 7.00 (1H, bs), 7.15-7.90 (14H, m)

MASS (APCI, m/z): 414 $(M+H)^+$

$[\alpha]_D^{27}$ +23.7° (c 0.5, EtOH)

Example 18

The following compounds were obtained according to the procedure of Example 17.

(1) 1-[(2S,3S)-2-benzyloxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxamide was prepared from (2S,3R)-2-benzyloxy-5-(1-naphthyl)-3-pentyl) methanesulfonate (obtained in Preparation 29(1))(1.99 g) and imidazole-4-carboxamide (0.67 g).

IR (neat): 3460, 3330, 3182, 1668, 1593 $cm^{-1}$

NMR ($CDCl_3$, d): 1.03 (3H, d, J=6.2Hz), 2.15-2.55 (2H, m), 2.74-3.03 (2H, m), 3.66 (1H, m), 3.86 (1H, m), 4.26 (1H, d, J=11.6Hz), 4.56 (1H, d, J=11.6Hz), 5.52 (1H, bs), 7.02 (1H, bs), 7.12-7.50 (10H, m), 7.71-7.88 (4H, m)

MASS (APCI, m/z): 414 $(M+H)^+$

$[\alpha]_D^{26}$ -21.1° (c 0.5, EtOH)

(2) 1-[(2S,3R)-2-(tert-butyldimethylsilyloxy)-5-phenyl-3-pentyl]imidazole-4-carboxamide was prepared from (2S,3S)-4-(tert-butyldimethylsilyloxy)-5-phenyl-3-pentyl methanesulfonate (obtained in Preparation 29(2)) and imidazole-4-carboxamide (obtained in Preparation 1) according to the procedure of Example 17.

IR (neat): 3465, 3332, 3188, 2935, 1672, 1599 $cm^{-1}$

NMR ($CDCl_3$, d): -0.24 (3H, s), 0.10 (3H, s), 0.88 (9H, s), 0.98 (3H, d, J=6.1Hz), 2.09 (1H, m), 2.20-2.45 (2H, m), 2.62 (1H, m), 3.77 (1H, m), 3.88 (1H, m), 5.47 (1H, bs), 6.98 (1H, bs), 7.06 (2H, d, J=6.4Hz), 7.20-7.33(3H, m), 7.38(1H, d, J=1.1Hz), 7.62(1H, d, J=1.1Hz)

MS (APCI, m/z): 388 $(M+H)^+$

$[\alpha]_D^{27}$ +29.3° (c 0.5, EtOH)

Example 19

The following compound was prepared by a similar procedure to that of Example 9.

(1) (S)-1-[1-hydroxy-4-phenyl-2-butyl]imidazole-4-carbohydrazide was prepared as an amorphous solid from the compound obtained in Example 13.

NMR (DMSO-$d_6$, $\delta$): 2.00-2.55 (4H, m), 3.63 (2H, t, J=5.2Hz), 4.10 (1H, m), 4.33 (2H, br), 5.01 (1H, t, J=5.3Hz), 7.10-7.35 (5H, m), 7.70 (1H, s), 7.77 (1H, s), 8.97 (1H, br s)

MASS: 275 $(M+H)^+$

(2) 1-[(2S,3R)-2-hydroxy-5-phenyl-3-pentyl]imidazole-4-carboxamide was prepared from the compound obtained in Example 18(2).

IR (KBr): 3336, 1658, 1593 $cm^{-1}$

NMR (DMSO-$d_6$, d): 0.87 (3H, d, J=6.0Hz), 2.00-2.40 (4H, m), 3.75-3.95 (2H, m), 5.08 (1H, d, J=4.8Hz), 7.07 (1H, bs), 7.10-7.30 (6H, m), 7.72 (1H, s), 7.74 (1H, s)

MS (APCI, m/z): 274$(M+H)^+$

$[\alpha]_D^{26}$ +43.5° (c 0.4, EtOH)

Example 20

A mixture of methyl 1-[(2S,3R)-2-benzyloxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxylate (obtained in Example 3(20)) (160 mg) in ammonium hydroxide (10 ml) and DMF (5 ml) was heated at 100 ℃ for 8 h in a sealed tube and then concentrated in vacuo. Flash chromatography (dichloromethane:methanol = 20:1) gave 1-[(2S,3R)-2-benzyloxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxamide (144 mg, 93.3%) as an oil.

Example 21

1-[(2S,3R)-2-benzyloxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxamide (obtained in Example 17 or 20) (5.07 g) was dissolved in a mixture of ethanol (300 ml) and cyclohexene (150 ml) and then palladium hydroxide (20% on carbon, 5.0 g) was added. The mixture

was heated under reflux for 3 days. After cooling, the catalyst was filtered and washed with ethanol. The combined filtrate and washings were concentrated in vacuo. Flash chromatography (dichloromethane : methanol = 10 : 1) gave 1-[(2S,3R)-2-hydroxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxamide (2.71 g, 68.4%) as a foam.

IR (KBr): 3334, 1666, 1593 $cm^{-1}$

NMR (DMSO-$d_6$, d): 0.88 (3H, d, J=6.2Hz), 2.10-2.40 (2H, m), 2.60-2.95 (2H, m), 3.83 (1H, m), 4.05 (1H, m), 5.09 (1H, d, J=4.9Hz), 7.10 (1H, bs), 7.25 (1H, d, J=6.3Hz), 7.34 (1H, bs), 7.42 (1H, t, J=7.6Hz), 7.49-7.54 (2H, m), 7.76-7.94 (5H, m)

MASS (APCI, m/z): 324 $(M+H)^+$

$[\alpha]_D^{27}$ +29.2° (c 0.5, EtOH)

Example 22

1-[(2S,3S)-2-hydroxy-5-(1-naphthyl)-3-pentyl]-imidazole-4-carboxamide was prepared from the compound obtained in Example 18(1) according to a similar procedure to Example 21.

IR (KBr): 3334, 1658, 1593 $cm^{-1}$

NMR (DMSO-$d_6$, d): 0.91 (3H, d, J=6.3Hz), 2.10-2.30 (2H, m), 2.60-3.05 (2H, m), 3.95 (1H, m), 4.13 (1H, m), 5.05 (1H, d, J=4.1Hz), 7.06 (1H, bs), 7.25-7.55 (5H, m), 7.75-7.95 (5H, m)

MASS (APCI, m/z): 324 $(M+H)^+$

$[\alpha]_D^{27}$ -22.4° (c 0.25, EtOH)

Example 23

The following compound was prepared by a similar procedure to that of Example 4.

(1) 1-[(2S,3R)-2-hydroxy-5-(2-methylphenyl)-3-pentyl]imidazole-4-carboxamide was prepared from the compound obtained in Example

3(8).

mp: 60-62℃

NMR ($CDCl_3$, $\delta$): 1.11 (3H,d,J=6Hz), 2.0-2.6 (5H,m), 2.20 (3H,s), 3.8-4.1 (2H,m), 5.47 (1H,s), 6.9-7.2 (5H,m), 7.46 (1H,d,J=1Hz), 7.73 (1H,d,J=1Hz)

MASS: 288 $(M+H)^+$

$[\alpha]_D^{25}$ = +110.5° (c 0.50, EtOH)

(2) 1-[(2S,3R)-2-hydroxy-5-(2-methoxyphenyl)-3-pentyl]-imidazole-4-carboxamide was prepared from the compound obtained in Exampoe 3(10).

NMR ($CDCl_3$, $\delta$): 1.09 (3H,d,J=6Hz), 2.0-2.7 (5H,m), 3.81 (3H,s), 3.9-4.0 (2H,m), 5.40 (1H,s), 6.8-7.3 (5H,m), 7.46 (1H,d,J=1Hz), 7.72 (1H,d,J=1Hz)

MASS: 304 $(M+H)^+$

$[\alpha]_D^{25}$ = +110.0° (c 0.50, EtOH)

(3) 1-[(2S,3R)-2-hydroxy-5-(2-hexyloxyphenyl)-3-pentyl]-imidazole-4-carboxamide was prepared from the compound obtained in Example 3(11).

NMR ($CDCl_3$, $\delta$): 0.8-1.0 (3H,m), 1.09 (3H,d,J=6Hz), 1.2-1.5 (6H,m), 1.7-1.9 (3H,m), 2.0-2.7 (4H,m), 3.8-4.0 (4H,m), 5.35 (1H,s), 6.8-7.3 (5H,m), 7.45 (1H,s), 7.69 (1H,s)

MASS: 374 $(M+H)^+$

$[\alpha]_D^{28}$ = +22.9° (c 0.50, EtOH)

(4) 1-[(2S,3R)-2-hydroxy-5-(2-hydroxyphenyl)-3-pentyl]-imidazole-4-carboxamide was prepared from the compound obtained in Example 3(13).

NMR (DMSO-$d_6$, $\delta$): 0.87 (3H,d,J=6Hz), 1.9-2.4 (4H,m), 3.7-4.0 (2H,m), 5.05 (1H,d,J=5Hz), 6.6-7.3 (6H,m), 7.71 (2H,s),

9.29 (1H,s)

MASS: 290 $(M+H)^+$

(5) 1-[(2S,3R)-2-hydroxy-5-(2,3-dimethylphenyl)-3-pentyl]-imidazole-4-carboxamide was prepared from the compound obtained in Example 3(14).

NMR ($CDCl_3$, $\delta$): 1.10 (3H,d,J=6Hz), 2.0-2.6 (5H,m), 2.11 (3H,s), 2.26 (3H,s), 3.9-4.0 (2H,m), 5.43 (1H,s), 6.8-7.1 (4H,m), 7.47 (1H,d,J=1Hz), 7.72 (1H,d,J=1Hz)

MASS: 302 $(M+H)^+$

$[\alpha]_D^{26}$ = +26.7° (c 0.50, EtOH)

(6) 1-[(2S,3R)-2-hydroxy-5-[2-(trifluoromethyl)phenyl]-3-pentyl]imidazole-4-carboxamide was prepared from the compound obtained in Example 3(15).

NMR ($CDCl_3$, $\delta$): 1.13 (3H,d,J=6Hz), 2.0-2.4 (3H,m), 2.5-2.8 (2H,m), 3.9-4.1 (2H,m), 5.42 (1H,s), 6.9-7.8 (7H,m)

MASS: 342 $(M+H)^+$

$[\alpha]_D^{25}$ = -0.70° (c 0.50, EtOH)

(7) Methyl 1-[(2S,3R)-2-hydroxy-5-(1-naphthyl)-3-pentyl]-imidazole-4-carboxylate was prepared from the compound obtained in Example 3(20).

NMR ($CDCl_3$, $\delta$): 1.09 (3H,d,J=6Hz), 1.9-2.6 (3H,m), 2.8-3.2 (2H,m), 3.92 (3H,s), 3.9-4.1 (2H,m), 7.1-7.9 (9H,m)

MASS: 339 $(M+H)^+$

(8) 1-{(2S,3R)-2-hydroxy-5-[2,3-(methylenedioxy)phenyl]-3-pentyl}imidazole-4-carboxamide was prepared from the compound obtained in Example 3(16).

NMR ($CDCl_3$, $\delta$): 1.11 (3H, d, J=6Hz), 2.1-2.7 (5H, m), 3.8-

4.1 (2H, m), 5.44 (1H, s), 5.92 (2H, s), 6.5-6.8 (3H, m), 6.99 (1H, s), 7.44 (1H, d, J=1Hz), 7.70 (1H, d, J=1Hz)

MS: 318 $(M+H)^+$

$[\alpha]_D^{27}$ = +29.3° (c 0.50, EtOH)

(9) 1-[(2S,3R)-2-hydroxy-5-(2-naphthyl)-3-pentyl]imidazole-4-carboxamide was prepared from the compound obtained in Example 3(18).

IR (KBr): 3340, 1658 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.10 (3H, d, J=6Hz), 2.1-2.4 (3H, m), 2.4-2.7 (1H, m), 2.7-2.9 (1H, m), 3.8-4.1 (2H, m), 5.46 (1H, s), 7.00 (1H, s), 7.2-7.9 (9H, m)

MS: 324 $(M+H)^+$

$[\alpha]_D^{26}$ = +55.4° (c 0.50, EtOH)

(10) 1-[(2S,3R)-2-hydroxy-6-(1-naphtyl)-3-hexyl]imidazole-4-carboxamide was prepared from the compound obtained in Example 3(19).

IR (KBr): 3340, 1658 $cm^{-1}$

NMR ($CDCl_3$, $\delta$): 1.08 (3H, d, J=6Hz), 1.5-2.2 (5H, m), 3.06 (2H, t, J=8Hz), 3.8-4.0 (2H, m), 5.48 (1H, s), 6.98 (1H, s), 7.2-8.0 (9H, m)

MS: 338 $(M+H)^+$

Example 24

A mixture of 1-[(2S,3R)-2-(benzyloxy)-5-(2-chlorophenyl)-3-pentyl]imidazole-4-carboxamide (obtained in Example 3(9))(40 mg) and iodotrimethylsilane (0.02 ml) in chloroform (1 ml) was stirred at room temperature for 2 hours. The mixture was poured into methanol and the whole was evaporated in vacuo. The residue was taken up in ethyl acetate, washed with water, aqueous sodium bisulfite and sodium bicarbonate, successively, and dried. The residue left after evaporation of solvent was purified by column chromatography on silica gel, eluting with a mixture of dichloromethane and methanol

(20 :1) to give a white powder of 1-[(2S,3R)-2-hydroxy-5-(2-chlorophenyl)-3-pentyl]imidazole-4-carboxamide (6.1 mg).

NMR ($CDCl_3$, $\delta$): 1.12 (3H,d,J=6Hz), 1.9-2.4 (3H,m), 2.5-2.7 (2H,m), 3.9-4.1 (2H,m), 5.40 (1H,s), 6.9-7.4 (5H,m), 7.49 (1H,d,J=1Hz), 7.72 (1H,d,J=1Hz)

MASS: 308 $(M+H)^+$

$[\alpha]_D^{28}$ = +17.9° (c 0.50, EtOH)

Example 25

1-[(2S,3R)-2-Hydroxy-5-(2,3-dichlorophenyl)-3-pentyl]-imidazole-4-carboxamide was prepared by a similar procedure to that of Example 24 from the compound obtained in Example 3(12).

mp: 70-75℃

NMR ($CDCl_3$, $\delta$): 1.13 (3H,d,J=6Hz), 1.98 (1H,d,J=5Hz), 2.1-2.4 (2H,m), 2.6-2.8 (2H,m), 3.9-4.1 (2H,m), 5.39 (1H,s), 6.9-7.4 (4H,m), 7.49 (1H,d,J=1Hz), 7.72 (1H,d,J=1Hz)

MASS: 342 $(M+H)^+$

$[\alpha]_D^{28}$ = +9.30° (c 0.50, EtOH)

Example 26

Methyl 1-[(2S,3R)-2-(benzyloxy)-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxylate was prepared by a similar procedure to that of Example 6 from methyl 4-imidazolecarboxylate and the compound obtained in Preparation 27.

NMR ($CDCl_3$, $\delta$): 1.06 (3H,d,J=6Hz), 2.1-2.6 (2H,m), 2.7-3.1 (2H,m), 3.6-3.7 (1H,m), 3.97 (3H,s), 3.9-4.1 (1H,m), 4.33 (1H,d,J=11Hz), 4.56 (1H,d,J=11Hz), 7.1-7.9 (14H,m)

MASS: 429 $(M+H)^+$

Example 27

1-[(2S,3R)-2-hydroxy-5-(1-naphthyl)-3-pentyl]imidazole-4-

carbonylguanidine acetic acid salt was prepared by a similar procedure to that of Example 8 from the compound obtained in Example 23(7).

NMR (DMSO-$d_6$ $\delta$): 0.90 (3H,d,J=6Hz), 1.88 (3H,s), 2.1-2.5 (2H,m), 2.6-3.0 (2H,m), 3.8-4.2 (2H,m), 5.15 (1H,br s), 7.2-8.0 (9H,m)

MASS: 366 $(M+H)^+$

$[\alpha]_D^{26}$ = +17.5° (c 0.50, EtOH)

Example 28

A mixture of 1-[(2S,3R)-2-hydroxy-5-(2-hydroxyphenyl)-3-pentyl]imidazole-4-carboxamide (obtained in Example 23(4))(4.1 mg), 1-bromo-3-phenylpropane (7 mg), and potassium carbonate (4 mg) in N,N-dimethylformamide (0.5 ml) was stirred overnight at room temperature. The mixture was taken up in ethyl acetate, washed twice with water, dried, and evaporated. The residue was purified by column chromatography on silica gel, eluting with a mixture of dichloromethane and methanol (20:1) to give a colorless gummy oil of 1-{(2S,3R)-2-hydroxy-5-[2-(3-phenylpropoxy)phenyl]-3-pentyl}imidazole-4-carboxamide (4.9 mg).

NMR ($CDCl_3$, $\delta$): 1.08 (3H, d, J=6Hz), 2.0-2.9 (9H, m), 3.9-4.0 (4H, m), 5.39 (1H, s), 6.7-7.4 (10H, m), 7.45 (1H, s), 7.71 (1H, s)

MS: 408 $(M+H)^+$

Example 29

A mixture of methyl 1-[(2S,3R)-2-hydroxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxylate (obtained in Example 23(7))(25 mg) and methylamine (40 % in water; 1 ml) in tetrahydrofuran (3 ml) was heated in a steel sealed tube at 120℃ overnight. The mixture was taken up in dichloromethane, washed with water, dried, and evaporated. The residue was purified by column chromatography on silica gel,

eluting with a mixture of dichloromethane and methanol (30:1) to give a white powder of N-methyl-1-[(2S,3R)-2-hydroxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxamide (18.6 mg).

NMR ($CDCl_3$, $\delta$): 1.07 (3H, d, J=6Hz), 2.1-2.5 (3H, m), 2.7-3.1 (2H, m), 3.01 (3H, d, J=7Hz), 3.8-4.0 (2H, m), 7.0-7.9 (10H, m)

MS: 338 $(M+H)^+$

$[\alpha]_D^{27}$ = +24.7° (c 0.50, EtOH)

Example 30

A mixture of methyl 1-[(2S,3R)-2-benzyloxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxylate (obtained in Example 3(20))(97 mg) and sodium hydroxide (12 mg) in ethanol (2 ml) and water (0.2 ml) was stirred at room temperature overnight. The solvent was evaporated and the residue was taken up in a mixture of ethyl acetate and water. The aqueous layer was separated, acidified to pH 3 with hydrochloric acid, and extracted with ethyl acetate. The extract was dried and evaporated to give a pale brown powder of 1-[(2S,3R)-2-benzyloxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxylic acid (84.5 mg).

NMR ($CDCl_3$, $\delta$): 1.07 (3H, d, J=6Hz), 2.2-2.6 (2H, m), 2.8-3.2 (2H, m), 3.5-3.7 (1H, m), 3.9-4.1 (1H, m), 4.34 (1H, d, J=12Hz), 4.55 (1H, d, J=12Hz), 7.1-7.9 (14H, m)

MS: 415 $(M+H)^+$

Example 31

A mixture of 1-[(2S,3R)-2-benzyloxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxylic acid (obtained in Example 30)(55 mg), methanesulfonamide (12.7 mg), 4-dimethylaminopyridine (24.3 mg), and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (51.2 mg) in N,N-dimethylformamide (2 ml) was stirred at room temperature for three days. Ethyl acetate and water were added, and

the whole was acidified to pH 3 with hydrochloric acid. The organic layer was dried and evaporated. The residue was purified by column chromatography on silica gel, eluting with a mixture of dichloromethane and methanol (20:1) to give a pale yellow gummy oil of N-methylsulfonyl-1-[(2S,3R)-2-benzyloxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxamide (18 mg).

NMR ($CDCl_3$, $\delta$): 1.05 (3H, d, J=6Hz), 2.2-2.5 (2H, m), 2.8-3.1 (2H, m), 3.40 (3H, s), 3.6-3.7 (1H, m), 3.9-4.1 (1H, m), 4.2-4.6 (2H, m), 7.0-7.9 (14H, m)

MS: 490 $(M-H)^-$

Example 32

N-methylsulfonyl-1-[(2S,3R)-2-hydroxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxamide was prepared from the compound obtained in Example 31 according to the procedure of Example 4.

NMR ($CDCl_3$+$CD_3OD$, $\delta$): 0.97 (3H, d, J=6Hz), 2.0-2.3 (2H, m), 2.7-3.1 (2H, m), 3.06 (3H, s), 3.8-4.1 (2H, m), 7.1-7.9 (9H, m)

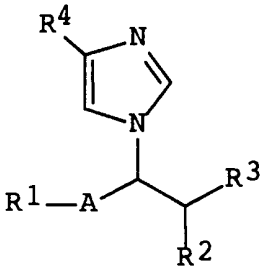
MS: 402 $(M+H)^+$

Industrial Applicability

The imidazole compounds of the present invention have ADA inhibitory activity and can thus elevate Ado concentration. Since Ado is effective for immunomodulation, especially immunosuppression, antiinflammation and treatment and prevention of various diseases, the imidazole compounds of the present invention are useful for treating or preventing diseases for which Ado is effective.

Claims

1. A compound of the formula



(I)

wherein $R^1$ is hydrogen, hydroxy, protected hydroxy, or aryl optionally substituted with suitable substituent(s);

$R^2$ is hydrogen or lower alkyl;

$R^3$ is hydroxy or protected hydroxy;

$R^4$ is cyano, (hydroxy)iminoamino(lower)alkyl, carboxy, protected carboxy, heterocyclic group optionally substituted with amino, or carbamoyl optionally substituted with suitable substituent(s); and

-A- is -Q- or -O-Q-, wherein Q is single bond or lower alkylene,

provided that when $R^2$ is lower alkyl, then $R^1$ is hydroxy, protected hydroxy, or aryl optionally substituted with suitable substituent(s),

its prodrug, or their salt.

2. The compound according to claim 1,

wherein $R^1$ is hydrogen, hydroxy, protected hydroxy, or aryl optionally substituted with suitable substituent(s) selected from the group consisting of halo(lower)alkyl, halogen, hydroxy, protected carboxy, carbamoyl, lower alkylenedioxy, lower alkoxy

optionally substituted with aryl, and lower alkyl optionally substituted with hydroxy or protected carboxy; and

$R^4$ is cyano, (hydroxy)iminoamino(lower)alkyl, carboxy, protected carboxy, heterocyclic group optionally substituted with amino, or carbamoyl optionally substituted with suitable substituent(s) selected from the group consisting of amino, hydroxy, lower alkyl, lower alkylsulfonyl and aminoimino(lower)alkyl optionally substituted with hydroxy.

3. The compound according to claim 2,

wherein $R^1$ is aryl optionally substituted with suitable substituent(s) selected from the group consisting of halo(lower)alkyl, halogen, hydroxy, protected carboxy, carbamoyl, lower alkylenedioxy, lower alkoxy optionally substituted with aryl, and lower alkyl optionally substituted with hydroxy or protected carboxy;

$R^4$ is carbamoyl optionally substituted with suitable substituent(s) selected from the group consisting of amino, hydroxy, lower alkyl, lower alkylsulfonyl and aminoimino(lower)alkyl optionally substituted with hydroxy; and

- A - is lower alkylene.

4. The compound according to claim 3,

wherein $R^1$ is phenyl or naphthyl, each of which are optionally substituted with suitable substituent(s) selected from the group consisting of halo(lower)alkyl, halogen, hydroxy, protected carboxy, carbamoyl, lower alkylenedioxy, lower alkoxy optionally substituted with aryl, and lower alkyl optionally substituted with hydroxy or protected carboxy; and

$R^4$ is carbamoyl.

5. The compound according to claim 2, which is a compound selected from the group consisting of:

(1) 1-(1-hydroxy-4-phenyl-2-butyl)imidazole-4-carboxamide;

(2) 1-[(2S)-2-hydroxy-5-phenyl-3-pentyl]imidazole-4-carboxamide;

(3) 1-[(2S,3R)-2-hydroxy-5-(2-benzyloxyphenyl)-3-pentyl]-imidazole-4-carboxamide;

(4) 1-[(2S,3R)-2-hydroxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carboxamide;

(5) 1-[(2S,3R)-2-hydroxy-5-(2-hexyloxyphenyl)-3-pentyl]-imidazole-4-carboxamide;

(6) 1-[(2S,3R)-2-hydroxy-5-(2-naphthyl)-3-pentyl]imidazole-4-carboxamide;

(7) 1-[(2S,3R)-2-hydroxy-5-(2-chlorophenyl)-3-pentyl]imidazole-4-carboxamide;

(8) 1-[(2S,3R)-2-hydroxy-5-(2,3-dichlorophenyl)-3-pentyl]-imidazole-4-carboxamide;

(9) 1-[(2S,3R)-2-hydroxy-5-(1-naphthyl)-3-pentyl]imidazole-4-carbonylguanidine; and

(10) 1-{(2S,3R)-2-hydroxy-5-[2-(3-phenylpropoxy)phenyl]-3-pentyl}imidazole-4-carboxamide.

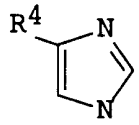
6. A pharmaceutical composition comprising the compound of claim 1 as an active ingredient and a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

7. A pharmaceutical composition having an adenosine deaminase inhibiting activity, which comprises the compound of claim 1 as an active ingredient and a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

8. A method for inhibiting adenosine deaminase, which comprises administering the compound of claim 1 to a mammal in need of the

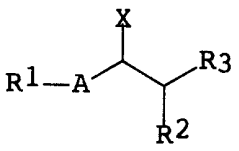
compound.

9. A process for producing the compound of claim 1, comprising reacting a compound of formula (III)



(III)

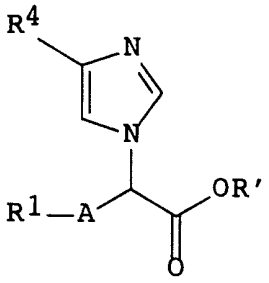
wherein $R^4$ is as defined above, with a compound of formula (IV)



(IV)

wherein $R^1$, $R^2$, $R^3$, and A are as defined above, and X is hydroxy or a leaving group, provided that $R^3$ is not hydroxy.

10. A process for producing the compound of claim 1, comprising reacting a compound of the formula (II)



(II)

wherein $R^1$ and $R^4$ are as defined above and R' is a hydroxy protective group, with a reducing agent.

11. Use of the compound of claim 1 for preparing a medicament for treating and/or preventing autoimmune diseases; inflammatory

conditions; organ or tissue allo-or xeno-transplant rejection; various leukemias; or diseases that arise from, or are aggravated by, insufficient blood flow through a particular organ or portion thereof.

# INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/JP 99/03939

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D233/90 C07D403/04 C07D405/06 C07F7/18 A61K31/415
A61K31/695

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 C07F A61K

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X,Y | CRISTALLI G ET AL: "Adenosine deaminase inhibitors: synthesis and structure-activity relationships of imidazole analogues of erythro-9-(2-hydroxy-3-nonyl)adenine" JOURNAL OF MEDICINAL CHEMISTRY, vol. 34, no. 3, March 1991 (1991-03), pages 1187-92, XP002119563 cited in the application the whole document<br>---<br>-/-- | 1-11 |

[X] Further documents are listed in the continuation of box C.

[X] 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.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 20 October 1999 | 05/11/1999 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Allard, M |

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Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Inter· onal Application No
PCT/JP 99/03939

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X,Y | CRISTALLI G ET AL: "Adenosine deaminase inhibitors: structure-activity relationships in 1-deazaadenosine and erythro-9-(2-hydroxy-3-nonyl)adenine analogs" DRUG DEVELOPMENT RESEARCH, vol. 28, no. 3, 1993, pages 253-8, XP002119564 cited in the application the whole document | 1-11 |
| Y | WO 98 02166 A (STATE OF RHODE ISLAND AND PROVIDENCE PLANTATIONS) 22 January 1998 (1998-01-22) cited in the application the whole document | 1-11 |
| Y | VARGEESE C ET AL: "Adenosine deaminase inhibitors. Synthesis and biological evaluation of putative metabolites of (+)-erythro-9-(2S-hydroxy-3R-nonyl) adenine" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 22, 28 October 1994 (1994-10-28), pages 3844-9, XP002119565 cited in the application the whole document | 1-11 |
| X | PIOTROVSKII L B ET AL: "Alkylation of imidazole-4(5)-carboxylic acid derivatives with ethylene oxide" RUSSIAN JOURNAL OF GENERAL CHEMISTRY, vol. 67, no. 5, May 1997 (1997-05), pages 801-4, XP002119566 compounds IV and VII | 1,2 |
| X | CHEMICAL ABSTRACTS, vol. 93, no. 15, 13 October 1980 (1980-10-13) Columbus, Ohio, US; abstract no. 142660j, ANON: "Ethyl 4(5)-imidazolecarboxylate (Code No. C-751) as an orally effective chemotherapeutic agent against leptospirosis" page 22; XP002119567 abstract -& "CHEMICAL ABSTRACTS, 1977-1981 CHEM. SUBSTANCE INDEX" XP002119574 page 26459CS, second column, first compound | 1,2,6,7 |

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# INTERNATIONAL SEARCH REPORT

national application No.
PCT/JP 99/03939

**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. [X] Claims Nos.: 8
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 8 is 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/composition.

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.

# INTERNATIONAL SEARCH REPORT

.ormation on patent family members

Interr ɔnal Application No
PCT/JP 99/03939

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9802166 A | 22-01-1998 | US 5703084 A | 30-12-1997 |
| | | CA 2261591 A | 22-01-1998 |
| | | EP 0936911 A | 25-08-1999 |