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(54) **Thiazole Derivative and use thereof as VAP-1 Inhibitor**

Thiazolderivate und deren Verwendung als VAP-1-Hemmer

Dérivé de thiazole et son utilisation en tant qu'inhibiteur VAP-1

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(56) References cited:
WO-A-2004/067521 **WO-A-2004/087138**
WO-A-2005/089755 **WO-A1-2008/066145**

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Description

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to a novel thiazole derivative (compounds represented by the below-mentioned formula (I) (hereinafter to be also referred to as compound (I)) and a pharmaceutically acceptable salt thereof, hereinafter to be sometimes collectively referred to as the compound of the present invention). In addition, the present invention relates to a vascular adhesion protein-1 inhibitor, a pharmaceutical agent for the prophylaxis or treatment of vascular adhesion protein-1 associated disease and the like, which comprise the compound of the present invention as an active ingredient.

BACKGROUND OF THE INVENTION

[0002] The vascular adhesion protein-1 (hereinafter to be abbreviated as VAP-1) is amine oxidase (semicarbazide sensitive amine oxidase, SSAO) abundantly existing in human plasma, which shows a remarkably increased expression in vascular endothelium and vascular smooth muscle in the inflammatory lesion. Although the physiological role of VAP-1 has not been elucidated until recently, VAP-1 gene was cloned in 1998, and VAP-1 was reported to be a membrane protein which, as an adhesion molecule, controls rolling and migration of lymphocytes and NK cells under the expression control of inflammatory cytokine. Although amine to be the substrate is unknown, it is considered to be methylamine produced in any part in the living body. It is also known that hydrogen peroxide and aldehyde produced due to the intramolecular amine oxidase activity are important factors for adhesion activity.

[0003] Recent reports have demonstrated that VAP-1 enzyme activity in plasma increases both in type I and type II diabetic patients, and the increase is particularly noticeable in diabetic patients affected with retinopathy complications (Diabetologia, 42 (1999) 233-237 (non-patent document 1), Diabetes Medicine, 16 (1999) 514-521 (non-patent document 2)).

[0004] Furthermore, VAP-1 has also been reported to relate to the following diseases (1) - (6): (1) cirrhosis, essential stabilized hypertension, diabetes, arteriosclerosis (see JP-A-61-239891 (patent document 1) and US Patent No. 4,888,283 (patent document 2)); (2) endothelial injury (in diabetes, arteriosclerosis and hypertension), cardiovascular disease relating to diabetes or uremia, pain relating to gout and arthritis, retinopathy (in diabetic patients) (see WO 1993/23023 (patent document 3)); (3) inflammatory disease or symptom (of binding tissue) (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and osteoarthritis or degenerative joint disease, Reiter's syndrome, Sjogren's syndrome, Behcet's syndrome, relapsing polychondritis, systemic lupus erythematosus, discoid lupus erythematodes, systemic sclerosis, eosinophilic fasciitis, polymyositis, dermatomyositis, polymyalgia rheumatica, vasculitis, temporal arthritis, polyarteritis nodosa, Wegener's granulomatosis, mixed connective tissue diseases and juvenile rheumatoid arthritis); inflammatory disease or symptom of gastrointestinal tract [Crohn's disease, ulcerative colitis, irritable bowel syndrome (spastic colon), fibrosis of liver, inflammation (stomatitis) of oral mucous membrane and recurrent aphthous stomatitis]; inflammatory disease or symptom of central nervous system (multiple sclerosis, Alzheimer's disease, and ischemia-reperfusion injury relating to ischemic stroke); pulmonary inflammatory disease or symptom (asthma, adult respiratory distress syndrome, chronic obliterative pulmonary diseases); (chronic) inflammatory disease or symptom of the skin (psoriasis, allergic lesion, lichen planus, pityriasis rosea, contact dermatitis, atopic dermatitis, pityriasis rubra pilaris); disease relating to carbohydrate metabolism (diabetes and complications derived from diabetes) including disease of microvessel and large vessel (arteriosclerosis, vascular retinopathy, retinopathy, nephropathy, nephrotic syndrome and neuropathy (multiple neuropathy, mononeuropathy and autonomic neuropathy), foot ulcer, articular problem and increase in infection risk); disease relating to abnormality in the differentiation or function of adipocyte or function of smooth muscle cell (arteriosclerosis and obesity); vascular disease [atherosclerosis, nonatherosclerotic disease, ischemic cardiac diseases including myocardial infarction and peripheral arterial obstruction, Raynaud's disease and Raynaud's phenomenon, thromboangiitis obliterans (Buerger's disease)]; chronic arthritis; inflammatory bowel disease; skin disease (see WO 2002/02090 (patent document 4), WO 2002/02541 (patent document 5) and US 2002/0173521 A (patent document 6)); (4) diabetes (see WO 2002/38152 (patent document 7)); (5) SSAO-mediated complications [diabetes (insulin-dependent diabetes (IDDM) and noninsulin-dependent diabetes (NIDDM)) and vascular complications (heart attack, angina pectoris, apoplexy, adamputation, blindness and renal failure)] (see WO 2002/38153 (patent document 8)); (6) vascular hyperpermeable disease [aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retina edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, ocular inflammatory disease caused by bacterial or viral infection, and by ophthalmic operation, ocular inflammatory disease caused by physical injury to the eye, symptom caused by ocular inflammatory disease including

itching, flare, edema and ulcer, erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis, angioneurotic edema, laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis and laryngitis or otitis media] (see WO 2004/087138 (patent document 9)); and the like.

[0005] WO 2004/067521 (patent document 10), WO 2004/087138 (patent document 9), WO 2006/011631 (patent document 11) and WO 2006/028269 (patent document 12) describe thiazole derivatives having specific structures and that they can be used for the prophylaxis or treatment of VAP-1 associated disease such as macular edema, vascular hyperpermeable disease and the like.

[0006] The thiazole derivatives having specific structures, which are described in WO 2004/067521 (patent document 10), WO 2004/087138 (patent document 9) and WO 2006/028269 (patent document 12), also conceptually encompass a compound having a hydrazino group or a hydrazinocarbonyl group at the molecular terminal. However, they do not disclose a novel compound having the specific functional group of the present invention (carbazic acid ester group, carbazic acid thioester group or semicarbazide group).

[0007] While WO 2008/066145 (patent document 13) describes a thiazole derivative having a particular structure, it does not disclose the novel compound of the present invention.

patent document 1: JP-A-61-239891
patent document 2: US Patent No. 4,888,283
patent document 3: WO 1993/23023
patent document 4: WO 2002/02090.
patent document 5: WO 2002/02541
patent document 6: US 2002/0173521 A
patent document 7: WO 2002/38152
patent document 8: WO 2002/38153
patent document 9: WO 2004/087138
patent document 10: WO 2004/067521
patent document 11: WO 2006/011631
patent document 12: WO 2006/028269
patent document 13: WO 2008/066145
non-patent document 1: Diabetologia, 42 (1999) 233-237
non-patent document 2: Diabetes Medicine, 16 (1999) 514-521

Disclosure of the Invention

Problems to be Solved by the Invention

[0008] The present invention aims to provide a novel thiazole derivative useful as a VAP-1 inhibitor, a pharmaceutical agent for the prophylaxis or treatment of VAP-1 associated diseases and the like.

Means of Solving the Problems

[0009] As a result of intensive studies, the present inventors have found that a thiazole derivative having a specific functional group (carbazic acid ester group, carbazic acid thioester group or semicarbazide group) at the molecular terminal has superior VAP-1 inhibitory action, is superior in enzyme selectivity and can eliminate feared side effects, and conducted further studies, which resulted in the completion of the present invention.

[0010] Accordingly, the present invention is as follows.

(1) A compound represented by the formula (I):

$$R^1\text{-NH-X-Y-Z} \qquad (I)$$

wherein
R^1 is acyl;
X is a divalent residue derived from optionally substituted thiazole;
Y is the formula (III):

$$J—L—M \qquad (III)$$

wherein J is a bond, C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene , - $-(CH_2)_n-O-$, $-(CH_2)_n-NH-$, $(CH_2)_n-$ CO-

or - $(CH_2)_n$-SO_2-(wherein n is an integer of 0 to 6);
L is a bond, -O-, -NH-, -CO- or -SO_2-;
M is a bond, C_1-C_6 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene, provided that when J is -$(CH_2)_n$-O-, L is not -O-, -NH- and -SO_2-, when J is -$(CH_2)_n$-NH-, L is not -O- and -NH-, when J is - $(CH_2)_n$-CO-, L is not -CO-, when J is -$(CH_2)_n$-SO_2-, L is not -O- and -SO_2- (wherein n is as defied above), Z is the formula (II):

A—B—D—E (II)

wherein A is a divalent residue derived from optionally substituted benzene;
B is -$(CH_2)_m$-O-CO- wherein m is an integer of 0 to 6;
D is -NR^3- wherein R^3 is hydrogen, lower alkyl, alkoxycarbonyl or acyl; and
E is optionally substituted amino; or a pharmaceutically acceptable salt thereof.
(2) The compound of the above-mentioned (1), wherein the compound represented by the aforementioned formula (I) is

4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl hydrazinecarboxylate,
4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl hydrazinecarboxylate,
2-(4-2-[2-(acetylamino)-1,3-thiazol-4-yl]ethylphenyl)ethyl hydrazinecarboxylate,
4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2-fluorobenzyl hydrazinecarboxylate,
4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-3-fluorobenzyl hydrazinecarboxylate,
4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2,3-difluorobenzyl hydrazinecarboxylate,
2-(4-{[2-(acetylamino)-1,3-thiazol-4-yl]methoxy}phenyl)ethyl hydrazinecarboxylate,
4-{2-[(hydrazinocarbonyl)oxy]ethyl}phenyl 2-(acetylamino)-1,3-thiazole-4-carboxylate,
2-[4-({[2-(acetylamino)-1, 3-thiazol-4-yl]carbonyl}amino)phenyl]ethyl hydrazinecarboxylate,
3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl hydrazinecarboxylate,
3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl hydrazinecarboxylate,
2-(3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl hydrazinecarboxylate,

or a pharmaceutically acceptable salt thereof.
(3) The compound of the above-mentioned (1), wherein the compound represented by the aforementioned formula (I) is 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl hydrazinecarboxylate or 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl hydrazinecarboxylate, or a pharmaceutically acceptable salt thereof.
(4) The compound of any one of the above-mentioned (1) to (3), or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical agent.
(5) A pharmaceutical composition comprising the compound of any one of the above-mentioned (1) to (3) or a pharmaceutically acceptable salt thereof as an active ingredient.
(6) The compound of any one of the above-mentioned (1) to (3) or a pharmaceutically acceptable salt thereof for use as a VAP-1 inhibitor.
(7) A pharmaceutical agent for use in the prophylaxis or treatment of VAP-1 associated disease, which agent comprises the compound of any one of the above-mentioned (1) to (3) or a pharmaceutically acceptable salt thereof as an active ingredient.
(8) The pharmaceutical agent for use according to the above-mentioned (7), wherein the aforementioned VAP-1 associated disease is macular edema (diabetic and nondiabetic macular edema), aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retina edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, ocular inflammatory disease caused by bacterial or viral infection, and by ophthalmic operation, ocular inflammatory disease caused by physical injury to the eye, symptom caused by ocular inflammatory disease including itching, flare, edema and ulcer, erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis (psoriasis, allergic lesion, lichen planus, pityriasis rosea, contact dermatitis, atopic dermatitis, pityriasis rubra pilaris), angioneurotic edema, laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis and laryngitis or otitis media, cirrhosis, essential stabilized hypertension, diabetes, arteriosclerosis, endothelial injury (in diabetes, arteriosclerosis and hypertension), cardiovascular disease relating to diabetes or uremia, pain relating to gout and arthritis, inflammatory disease or symptom of binding tissue (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and osteoarthritis or degenerative joint disease, Reiter's syndrome, Sjogren's syndrome, Behcet's syndrome, relapsing polychondritis, systemic lupus erythematosus, discoid lupus erythematodes, systemic sclerosis,

eosinophilic fasciitis, polymyositis, dermatomyositis, polymyalgia rheumatica, vasculitis, temporal arthritis, polyarteritis nodosa, Wegener's granulomatosis, mixed connective tissue diseases and juvenile rheumatoid arthritis), inflammatory disease or symptom of gastrointestinal tract [Crohn's disease, ulcerative colitis, irritable bowel syndrome (spastic colon), fibrosis of the liver, inflammation of the oral mucous membrane (stomatitis and recurrent aphthous stomatitis)], inflammatory disease or symptom of central nervous system (multiple sclerosis, Alzheimer's disease, and ischemia-reperfusion injury relating to ischemic stroke), pulmonary inflammatory disease or symptom (asthma, adult respiratory distress syndrome, chronic obliterative pulmonary diseases), disease relating to carbohydrate metabolism (diabetes and complications derived from diabetes (diabetic neuropathy, diabetic nephropathy)) including disease of microvessel and large vessel (arteriosclerosis, retinopathy, nephropathy, nephrotic syndrome and neuropathy (multiple neuropathy, mononeuropathy and autonomic neuropathy), foot ulcer, articular problem and increase in infection risk), disease relating to abnormality in the differentiation or function of adipocyte or function of smooth muscle cell (arteriosclerosis and obesity), vascular disease [atheromatous atherosclerosis, nonatheromatous atherosclerotic disease, ischemic cardiac diseases including myocardial infarction and peripheral arterial obstruction, Raynaud's disease and Raynaud's phenomenon, thromboangiitis obliterans (Buerger's disease)], chronic arthritis, inflammatory bowel disease, or SSAO-mediated complications [diabetes (insulin-dependent diabetes (IDDM) and noninsulin-dependent diabetes (NIDDM)) and vascular complications (heart attack, angina pectoris, apoplexy, amputation, blindness and renal failure)], ophthalmic disease associated with hypoxia or ischemia [retinopathy of prematurity, proliferative diabetic retinopathy, polypoidal choroidal vasculopathy, retinal angiomatous proliferation, retinal artery occlusion, retinal vein occlusion, Coats' disease, familial exudative vitreoretinopathy, pulseless disease (Takayasu's disease), Eales disease, antiphospholipid antibody syndrome, leukemic retinopathy, blood hyperviscosity syndrome, macroglobulinemia, interferon-associated retinopathy, hypertensive retinopathy, radiation retinopathy, corneal epithelial stem cell deficiency] or cataract.

(9) Use of the compound of any one of the above-mentioned (1) to (3), or a pharmaceutically acceptable salt thereof, for the production of a pharmaceutical agent for use as a VAP-1 inhibitor.

(10) Use of the compound of any one of the above-mentioned (1) to (3), or a pharmaceutically acceptable salt thereof, for the production of a pharmaceutical agent for the prophylaxis or treatment of a VAP-1 associated disease.

(11) Use of the above-mentioned (10), wherein the aforementioned VAP-1 associated disease is macular edema (diabetic and nondiabetic macular edema), aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retina edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, ocular inflammatory disease caused by bacterial or viral infection, and by ophthalmic operation, ocular inflammatory disease caused by physical injury to the eye, symptom caused by ocular inflammatory disease including itching, flare, edema and ulcer, erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis (psoriasis, allergic lesion, lichen planus, pityriasis rosea, contact dermatitis, atopic dermatitis, pityriasis rubra pilaris), angioneurotic edema, laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis and laryngitis or otitis media, cirrhosis, essential stabilized hypertension, diabetes, arteriosclerosis, endothelial injury (in diabetes, arteriosclerosis and hypertension), cardiovascular disease relating to diabetes or uremia, pain relating to gout and arthritics, inflammatory disease or symptom of binding tissue (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and osteoarthritis or degenerative joint disease, Reiter's syndrome, Sjogren's syndrome, Behcet's syndrome, relapsing polychondritis, systemic lupus erythematosus, discoid lupus erythematodes, systemic sclerosis, eosinophilic fasciitis, polymyositis, dermatomyositis, polymyalgia rheumatica, vasculitis, temporal arthritis, polyarteritis nodosa, Wegener's granulomatosis, mixed connective tissue diseases and juvenile rheumatoid arthritis), inflammatory disease or symptom of gastrointestinal tract [Crohn's disease, ulcerative colitis, irritable bowel syndrome (spastic colon), fibrosis of the liver, inflammation of the oral mucous membrane (stomatitis and recurrent aphthous stomatitis)], inflammatory disease or symptom of central nervous system (multiple sclerosis, Alzheimer's disease, and ischemia-reperfusion injury relating to ischemic stroke), pulmonary inflammatory disease or symptom (asthma, adult respiratory distress syndrome, chronic obliterative pulmonary diseases), disease relating to carbohydrate metabolism (diabetes and complications derived from diabetes (diabetic neuropathy, diabetic nephropathy)) including disease of microvessel and large vessel (arteriosclerosis, retinopathy, nephropathy, nephrotic syndrome and neuropathy (multiple neuropathy, mononeuropathy and autonomic neuropathy), foot ulcer, articular problem and increase in infection risk), disease relating to abnormality in the differentiation or function of adipocyte or function of smooth muscle cell (arteriosclerosis and obesity), vascular disease [atheromatous atherosclerosis, nonatheromatous atherosclerotic disease, ischemic cardiac diseases including myocardial infarction and peripheral arterial obstruction, Raynaud's disease and Raynaud's phenomenon, thromboangiitis obliterans (Buerger's disease)], chronic arthritis, inflammatory bowel disease, or SSAO-mediated complications [diabetes (insulin-dependent diabetes (IDDM) and noninsulin-dependent diabetes

(NIDDM)) and vascular complications (heart attack, angina pectoris, apoplexy, amputation, blindness and renal failure)], ophthalmic disease associated with hypoxia or ischemia [retinopathy of prematurity, proliferative diabetic retinopathy, polypoidal choroidal vasculopathy, retinal angiomatous proliferation, retinal artery occlusion, retinal vein occlusion, Coats' disease, familial exudative vitreoretinopathy, pulseless disease (Takayasu's disease), Eales disease, antiphospholipid antibody syndrome, leukemic retinopathy, blood hyperviscosity syndrome, macroglobulinemia, interferon-associated retinopathy, hypertensive retinopathy, radiation retinopathy, corneal epithelial stem cell deficiency] or cataract.

Effect of the Invention

[0011] The compound of the present invention has superior VAP-1 inhibitory activity and superior enzyme selectivity, and therefore, can remove side effects and the like which are undesirable as a pharmaceutical product. Therefore, the compound is useful as a VAP-1 inhibitor, a pharmaceutical agent for the prophylaxis or treatment of a VAP-1 associated disease and the like.

Best Mode for Carrying out the Invention

[0012] The terms used for the present invention in the above- and below-mentioned descriptions of the present specification are explained in detail in the following.

[0013] The term "lower" is used to mean a group having a carbon number of 1 to 6, preferably 1 to 4, unless otherwise specified.

[0014] Examples of the "lower alkyl" include a straight chain or branched chain alkyl having a carbon number of 1 to 6 (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl and hexyl) and the like. Among these, C_1-C_4 alkyl is more preferable.

[0015] Examples of the "lower alkylene" include a straight chain or branched chain alkylene having a carbon number of 1 to 6 (e.g., methylene, ethylene, trimethylene, propylene, ethylidene and propylidene) and the like. Among these, C_1-C_4 alkylene is more preferable.

[0016] Examples of the "lower alkenylene" include a straight chain or branched chain alkenylene having a carbon number of 2 to 6 (e.g., vinylene, 1-propenylene, 1-methyl-1-propenylene, 2-methyl-1-propenylene, 2-propenylene, 2-butenylene, 1-butenylene, 3-butenylene, 2-pentenylene, 1-pentenylene, 3-pentenylene, 4-pentenylene, 1,3-butadienylene, 1,3-pentadienylene, 2-penten-4-ynylene, 2-hexenylene, 1-hexenylene, 5-hexenylene, 3-hexenylene, 4-hexenylene, 3,3-dimethyl-1-propenylene, 2-ethyl-1-propenylene, 1,3,5-hexatrienylene, 1,3-hexadienylene, 1,4-hexadienylene) and the like. Among these, C_2-C_4 alkenylene is more preferable.

[0017] The above-mentioned lower alkenylene may be an E-form or Z-form. When the compound of the present invention has a lower alkenylene moiety, the compound of the present invention encompasses any stereoisomer wherein the lower alkenylene moiety is an E-structure or Z-structure.

[0018] Examples of the "lower alkynylene" include a straight chain or branched chain alkynylene having a carbon number of 2 to 6, which has 1 to 3 triple bonds (e.g., ethynylene, 1-propynylene, 1-methyl-1-propynylene, 2-methyl-1-propynylene, 2-propynylene, 2-butynylene, 1-butynylene, 3-butynylene, 2-pentynylene, 1-pentynylene, 3-pentynylene, 4-pentynylene, 2-pentyn-4-ynylene, 2-hexynylene, 1-hexynylene, 5-hexynylene, 3-hexynylene, 4-hexynylene, 3,3-diethyl-1-propynylene, 2-ethyl-1-propynylene) and the like. Among these, C_2-C_4 alkynylene is more preferable.

[0019] Examples of the "aryl" include C_6-C_{10} aryl (e.g., phenyl and naphthyl) and the like, where the "aryl" may be substituted by 1 to 3 substituents and the position of substitution is not particularly limited.

[0020] Examples of the "aralkyl" include aralkyl wherein the aryl moiety has a carbon number of 6 to 10 [that is, the aryl moiety is C_6-C_{10} aryl of the above-mentioned "aryl"], and the alkyl moiety has a carbon number of 1 to 6 [that is, the alkyl moiety is C_1-C_6 alkyl of the above-mentioned "lower alkyl"] (e.g., benzyl, phenethyl, 1-naphthylmethyl, 2-naphthylmethyl, 3-phenylpropyl, 4-phenylbutyl and 5-phenylpentyl) and the like.

[0021] Examples of the "cyclo lower alkyl" include cycloalkyl having a carbon number of 3 to 6 (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) and the like.

[0022] Examples of the "cyclo lower alkoxycarbonyl" include cycloalkoxycarbonyl wherein the cycloalkyl moiety has a carbon number of 3 to 6 (e.g., cyclopropyloxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl) and the like.

[0023] Examples of the "heterocycle" include "aromatic heterocycle" and "non-aromatic heterocycle". Examples of the "aromatic heterocycle" include a 5- to 10-membered aromatic heterocycle containing, besides carbon atoms, 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur atom and the like, for example, thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyridazine, pyrimidine, pyrazine and the like. Examples of the "non-aromatic heterocycle" include a 5- to 10-membered non-aromatic heterocycle containing, besides carbon atoms, 1 to 3 hetero atom selected from nitrogen, oxygen and sulfur atom and the like, for example, pyrrolidine,

imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, morpholine, thiomorpholine, dioxolane, oxazolidine, thiazolidine, triazolysine and the like.

[0024] Examples of the "acyl" include alkylcarbonyl, arylcarbonyl and the like.

[0025] Examples of the "alkylcarbonyl" include alkylcarbonyl wherein the alkyl moiety has 1 to 6 carbon atoms [that is, the alkyl moiety is C_1-C_6 alkyl of the above-mentioned "lower alkyl"] (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl and decanoyl) and the like.

[0026] Examples of the "arylcarbonyl" include arylcarbonyl wherein the aryl moiety has 6 to 10 carbon atoms [that is, the aryl moiety is C_6-C_{10} aryl of the above-mentioned "aryl"] (e.g., benzoyl and naphthoyl) and the like.

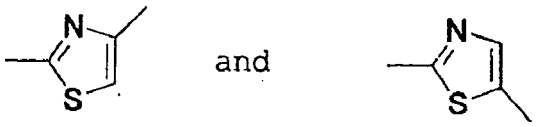
[0027] Examples of the "alkoxycarbonyl" include alkyloxycarbonyl, aralkyloxycarbonyl and the like.

[0028] Examples of the "alkyloxycarbonyl" include alkyloxycarbonyl wherein the alkyl moiety has a carbon number of 1 to 10 (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl and decyloxycarbonyl etc.) and the like.

[0029] Examples of the "aralkyloxycarbonyl" include aralkyloxycarbonyl wherein the aryl moiety has a carbon number of 6 to 10 [that is, the aryl moiety is C_6-C_{10} aryl of the above-mentioned "aryl"], and the alkyl moiety has a carbon number of 1 to 6 [that is, the alkyl moiety is C_1-C_6 alkyl of the above-mentioned "lower alkyl"] (e.g., benzyloxycarbonyl, phenethyloxycarbonyl, 1-naphthylmethyloxycarbonyl, 2-naphthylmethyloxycarbonyl, 3-phenylpropyloxycarbonyl, 4-phenylbutyloxycarbonyl and 5-phenylpentyloxycarbonyl etc.) and the like.

[0030] Examples of the "acyl" for R^1 in the formula (I) include those defined above and the like, preferably alkylcarbonyl (the alkylcarbonyl is as defined above) and the like, particularly preferably acetyl and the like.

[0031] Examples of the "divalent residue derived from the optionally substituted thiazole" for X in the formula (I) include



[0032] The "thiazole" may have a substituent, and the position of substitution is not particularly limited. Examples of the "substituent" of the above-mentioned "optionally substituted thiazole" include a group described in the following (1) - (12) and the like.

(1) halogen (e.g., fluorine, chlorine, bromine);

(2) alkoxycarbonyl defined above (e.g., ethoxycarbonyl);

(3) optionally substituted aryl (aryl is as defined above, and may be substituted by -SO_2-(lower alkyl) wherein the lower alkyl is as defined above and the like, where the position of substitution is not particularly limited) (e.g., phenyl and 4-(methylsulfonyl)phenyl);

(4) a group of the formula: -$CONR^aR^b$ wherein R^a is hydrogen, lower alkyl, aryl or aralkyl, R^b is hydrogen, lower alkyl, aryl or aralkyl, where the lower alkyl, aryl and aralkyl are as defined above (e.g., N-methylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl and N-benzylaminocarbonyl);

(5) a group of the formula: -CONH-$(CH_2)_k$-aryl wherein k is an integer of 0 to 6; aryl is as defined above, optionally has 1 to 5 substituents selected from the group consisting of -NO_2, -SO_2-(lower alkyl) wherein the lower alkyl is as defined above, -CF_3 and -O-aryl wherein aryl is as defined above, where the position of substitution is not particularly limited;

(6) a group of the formula: -CONH-$(CH_2)_s$-heterocycle wherein s is an integer of 0 to 6; and heterocycle is as defined above (e.g., pyridine);

(7) a group of the formula: -CO-heterocycle wherein heterocycle is as defined above (e.g., pyrrolidine, piperidine, piperazine, thiomorpholine), and heterocycle optionally has 1 to 5 substituents selected from the group consisting of -CO-(lower alkyl) wherein the lower alkyl is as defined above, - CO-O-(lower alkyl) wherein the lower alkyl is as defined above, -SO_2-(lower alkyl) wherein the lower alkyl is as defined above, oxo (i.e., =0) and a group of the formula: -$CONR^cR^d$ wherein R^c is hydrogen, lower alkyl, aryl or aralkyl, R^d is hydrogen, lower alkyl, aryl or aralkyl, and lower alkyl, aryl and aralkyl are as defined above, where the position of substitution is not particularly limited;

(8) a group of the formula: -$(CH_2)_t$-aryl wherein t is an integer of 1 to 6; aryl is as defined above, and optionally has 1 to 5 substituents selected from the group consisting of -S-(lower alkyl) wherein lower alkyl is as defined above, -SO_2-(lower alkyl) wherein lower alkyl is as defined above, -SO_2-NR^vR^w wherein R^v is hydrogen, lower alkyl, aryl or aralkyl, R^w is hydrogen, lower alkyl, aryl or aralkyl, and lower alkyl, aryl and aralkyl are as defined above, -CO_2-(lower alkyl) wherein lower alkyl is as defined above, -NHCO-O-(lower alkyl) wherein lower alkyl is as defined above

and a group of the formula: -$CONR^eR^f$ wherein R^e is hydrogen, lower alkyl, aryl or aralkyl, R^f is hydrogen, lower alkyl, aryl or aralkyl, and lower alkyl, aryl and aralkyl are as defined above, where the position of substitution is not particularly limited;

(9) a group of the formula: -$(CH^2)_o$-heterocycle wherein o is an integer of 0 to 6; heterocycle is as defined above (e.g., pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine), and optionally has 1 to 5 substituents selected from the group consisting of oxo (that is, =O); -CO-(lower alkyl) wherein lower alkyl is as defined above; -CO-O-(lower alkyl) wherein lower alkyl is as defined above; -SO_2-(lower alkyl) wherein lower alkyl is as defined above; -CO-(heterocycle) wherein heterocycle is as defined above (e.g., pyrrolidine, piperazine and morpholine), and optionally has 1 to 5 substituents selected from the group consisting of lower alkyl (lower alkyl is as defined above) and halogen (e.g., fluorine, chlorine, bromine), where the position of substitution is not particularly limited; and a group of the formula: -$CONR^gR^h$ wherein R^g is hydrogen, lower alkyl, aryl or aralkyl, R^h is hydrogen, lower alkyl, aryl or aralkyl, and lower alkyl, aryl and aralkyl are as defined above, where the position of substitution is not particularly limited;

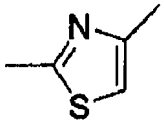
(10) a group of the formula: -$(CH_2)_p$-NR^iR^j wherein p is an integer of 0 - 6; R^i is hydrogen, acyl, lower alkyl, aryl or aralkyl, R^j is hydrogen, acyl, lower alkyl, aryl or aralkyl, and acyl, lower alkyl, aryl and aralkyl are as defined above, and lower alkyl optionally has 1 to 5 substituents selected from the group consisting of a group of the formula: -$CONR^kR^1$ wherein R^k is hydrogen, lower alkyl, aryl or aralkyl, R^1 is hydrogen, lower alkyl, aryl or aralkyl, and lower alkyl, aryl and aralkyl are as defined above, where the position of substitution is not particularly limited;

(11) a group of the formula: -CON(H or lower alkyl)-$(CHR^m)_q$-T wherein q is an integer of 0 to 6; lower alkyl is as defined above; R^m is hydrogen, aralkyl defined above or alkyl defined above (particularly lower alkyl), these are optionally substituted by 1 to 3 substituents selected from the group consisting of -OH and -$CONH_2$, where the position of substitution is not particularly limited; T is hydrogen; a group of the formula: -$CONR^nR^o$ wherein R^n is hydrogen, lower alkyl, aryl or aralkyl, R° is hydrogen, lower alkyl, aryl or aralkyl, and lower alkyl, aryl and aralkyl are as defined above; -NH-CO-R^P wherein R^P is lower alkyl defined above or aralkyl defined above; -NH-SO_2-(lower alkyl) wherein lower alkyl is as defined above; -SO_2-(lower alkyl) wherein lower alkyl is as defined above; -heterocycle wherein heterocycle is as defined above (e.g., pyridine, pyrrolidine and morpholine), optionally has 1 to 3 substituents (e.g., oxo (that is, =O)), where the position of substitution is not particularly limited; or -CO-(heterocycle) wherein heterocycle is as defined above (e.g., piperidine and morpholine)); and

(12) a group of the formula: -$(CH_2)_r$-CO-NR^tR^u wherein r is an integer of 1 to 6; R^t is hydrogen, lower alkyl, aryl or aralkyl, R^u is hydrogen, lower alkyl, aryl or aralkyl, and lower alkyl, aryl and aralkyl are as defined above.

[0033] The position of substitution on aryl or heterocycle may be any and is not particularly limited. Preferable "substituent" of the above-mentioned "optionally substituted thiazole" is methylsulfonylbenzyl, sulfamoylbenzyl (e.g., 4-sulfamoylbenzyl) and the like. The position of substitution of the methylsulfonyl group, sulfamoyl group and the like is not particularly limited.

[0034] As the "divalent residue derived from thiazole" moiety of the "divalent residue derived from optionally substituted thiazole" for X in the formula (I),

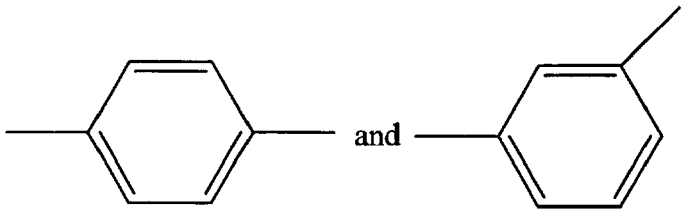


is preferable. As the "substituent" of the "divalent residue derived from optionally substituted thiazole", methylsulfonylbenzyl, sulfamoylbenzyl (e.g., 4-sulfamoylbenzyl) and the like are preferable.

[0035] The C_1-C_6 alkylene, C_2-C_6 alkenylene and C_2-C_6 alkynylene for J or M of the formula (III): J-L-M for Y in the formula (I) may be those defined above.

[0036] Specific examples of the formula (III): J-L-M for Y in the formula (I) include - -$(CH_2)_n$-, - $(CH_2)_n$-NH- $(CH_2)_{n'}$-, -$(CH_2)_n$-O-$(CH_2)_{n'}$-, -$(CH_2)_n$-CO-O- $(CH_2)_{n'}$-, -$(CH_2)_n$-O-CO-$(CH_2)_{n'}$-, $(CH_2)_n$-CO-NH-$(CH_2)_{n'}$-, -$(CH_2)_n$-NH-CO-$(CH_2)_{n'}$-, -$(CH_2)_n$-SO_2-NH-$(CH_2)_{n'}$- and -$(CH_2)_n$-NH-SO_2-$(CH_2)_{n'}$- (wherein n and n' are each an integer of 0 to 6, n is preferably an integer of 0 to 3, and n' is preferably an integer of 0 to 3). Among these, -$(CH_2)_n$-, -$(CH_2)_n$-NH-$(CH_2)_{n'}$-, -$(CH_2)_n$-O-$(CH_2)_{n'}$, -$(CH_2)_n$-CO-O-$(CH_2)_{n'}$-, and -$(CH_2)_n$-CO-NH-$(CH_2)_{n'}$- are preferable, and -$(CH_2)_n$-is particularly preferable. Specifically, - $(CH_2)_2$-, -CH_2-CO-, -CH_2-NH-, -CH_2-O-, -CO-O-, -CO-NH- can also be mentioned.

[0037] Specific examples of the divalent residue derived from optionally substituted benzene for A in the formula (II): A-B-D-E for Z in the formula (I) include



[0038] "Benzene" may have a substituent, and the position of substitution is not particularly limited. Examples of the "substituent" of the above-mentioned "optionally substituted benzene" include halogen (e.g., fluorine, chlorine, bromine), lower alkyl (e.g., methyl, ethyl), lower alkoxy (e.g., methoxy), acyl (e.g., acetyl) and halogenated alkyl (e.g., trifluoromethyl).

[0039] Examples of the C_1-C_6 alkyl and acyl for R^2 of -$(CH_2)_1$-NR^2-CO- represented by B include those defined above.

[0040] m in -$(CH_2)_m$-O-CO- represented by B is an integer of 0 to 6 (preferably 0 to 3).

[0041] Specific examples of B include -O-CO-, -CH_2-O-CO-, -$(CH_2)_2$-O-CO- and -$(CH_2)_3$-O-CO-.

[0042] Examples of the C_1-C_6 alkyl, alkoxycarbonyl and acyl for R^3 in -NR^3- represented by D include those defined above. Specific examples of D include -NH- and -N(CH_3)-.

[0043] Examples of the "optionally substituted amino" for E include unsubstituted amino, and amino substituted by 1 or 2 substituents. The "optionally substituted amino" is represented by the formula -NR^4R^5.

[0044] Examples of R^4 and R^5 include groups of lower alkyl, acyl (particularly, lower alkylcarbonyl, hydroxy lower alkylcarbonyl), alkoxycarbonyl, hydroxyalkoxycarbonyl, aryl, aralkyl, cyclo lower alkyl, cyclo lower alkoxycarbonyl, sulfuryl, sulfinyl, phosphoryl and heterocycle, which are each unsubstituted or optionally substituted by hydroxy etc., hydrogen and the like. The lower alkyl, acyl (particularly, lower alkylcarbonyl), alkoxycarbonyl, aryl, aralkyl, cyclo lower alkyl, cyclo lower alkoxycarbonyl and heterocycle are as defined above.

[0045] Specific examples of R^4 and R^5 include hydrogen, lower alkyl (e.g., methyl, ethyl), acetyl, butanoyl, decanoyl, 3-hydroxypropanoyl, 6-hydroxyhexanoyl, ethoxycarbonyl, butoxycarbonyl, decyloxycarbonyl and 2-hydroxyethoxycarbonyl.

[0046] The amino moiety of "optionally substituted amino" for E may be protected (i.e., substituted) according to the method described in "Protective Groups in Organic Synthesis 3rd Edition" (John Wiley and Sons, 1999), and the like. R^4 and R^5 may be the same or different.

[0047] As the -B-D-E part (molecule terminal) of the formula (II): A-B-D-E which is shown by Z in the formula (I), B is -O-CO-, -CH_2-O-CO-, -$(CH_2)_2$-O-CO- or -$(CH_2)_3$-O-CO-; D is -NH-; and E is -NH_2 and the like. Specifically, the -B-D-E part is, for example, -O-CO-NH-NH_2, -CH_2-O-CO-NH-NH_2, -$(CH_2)_2$-O-CO-NH-NH_2 or $(CH_2)_3$-O-CO-NH-NH_2. Preferred is -O-CO-NH-NH_2, -CH_2-O-CO-NH-NH_2, - -$(CH_2)_2$-O-CO-NH-NH_2 or, - $(CH_2)_3$-O-CO-NH-NH_2. Particularly preferred is -CH_2-O-CO-NH-NH_2.

[0048] Examples of compound (I) include

4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl hydrazinecarboxylate,
4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl hydrazinecarboxylate,
2-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl hydrazinecarboxylate,
4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2-fluorobenzyl hydrazinecarboxylate,
4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-3-fluorobenzyl hydrazinecarboxylate,
4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2,3-difluorobenzyl hydrazinecarboxylate,
2-(4-{[2-(acetylamino)-1,3-thiazol-4-yl]methoxy}phenyl)ethyl hydrazinecarboxylate,
4-{2-[(hydrazinocarbonyl)oxy]ethyl}phenyl 2-(acetylamino)-1,3-thiazole-4-carboxylate,
2-[4-({[2-(acetylamino)-1,3-thiazol-4-y1]carbonyl}amino)phenyl]ethyl hydrazinecarboxylate,
3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl hydrazinecarboxylate,
3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl hydrazinecarboxylate,
2-(3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl hydrazinecarboxylate,

can be mentioned.

[0049] Preferred are 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl hydrazinecarboxylate and 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl hydrazinecarboxylate.

[0050] When compound (I) has an asymmetric carbon atom in the structure, the present invention encompasses all enantiomers and diastereomers.

[0051] Compound (I) can also be converted to a pharmaceutically acceptable salt. The pharmaceutically acceptable salt in the present invention is not particularly limited as long as it is a nontoxic pharmaceutically acceptable general salt, and a salt with an inorganic or organic base, acid addition salt and the like can be mentioned. Examples of the salt

with an inorganic or organic base include alkali metal salt (e.g., sodium salt, potassium salt and the like), alkaline earth metal salt (e.g., calcium salt, magnesium salt and the like), ammonium salt, and amine salt (e.g., triethylamine salt, N-benzyl-N-methylamine salt and the like) and the like. Examples of the acid addition salt include salts derived from mineral acid (e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, phosphoric acid, metaphosphoric acid, nitric acid and sulfuric acid), and salts derived from organic acid (e.g., tartaric acid, acetic acid, trifluoroacetic acid, citric acid, malic acid, lactic acid, fumaric acid, maleic acid, benzoic acid, glycol acid, gluconic acid, succinic acid and arylsulfonic acid (e.g., p-toluenesulfonic acid)) and the like.

[0052] The compound of the present invention can be used as a prodrug for the below-mentioned pharmaceutical agent and the like. The term "prodrug" means any compound that can be converted to a VAP-1 inhibitor in the body after administration. The prodrug may be any optionally pharmaceutically acceptable prodrug of the compound of the present invention.

[0053] The compound of the present invention can be used as an active ingredient of a pharmaceutical agent such as a VAP-1 inhibitor, a pharmaceutical agent for the prophylaxis or treatment of a VAP-1 associated disease and the like.

[0054] The "vascular adhesion protein-1 (VAP-1) associated disease" is not particularly limited as long as it is a disease wherein VAP-1 is related to the expression and/or progress of the disease, and includes a disease selected from the group consisting of vascular hyperpermeable disease [e.g., macular edema (e.g., diabetic and nondiabetic macular edema), aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retina edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, ocular inflammatory disease caused by bacterial or viral infection, and by ophthalmic operation, ocular inflammatory disease caused by physical injury to the eye, symptom caused by ocular inflammatory disease including itching, flare, edema and ulcer, erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis (e.g., psoriasis, allergic lesion, lichen planus, pityriasis rosea, contact dermatitis, atopic dermatitis, pityriasis rubra pilaris), angioneurotic edema, laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis and laryngitis or otitis media], cirrhosis, essential stabilized hypertension, diabetes, arteriosclerosis, endothelial injury (in, for example, diabetes, arteriosclerosis and hypertension), cardiovascular disease relating to diabetes or uremia, pain relating to gout and arthritis, inflammatory disease or symptom of binding tissue (e.g., rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and osteoarthritis or degenerative joint disease, Reiter's syndrome, Sjogren's syndrome, Behcet's syndrome, relapsing polychondritis, systemic lupus erythematosus, discoid lupus erythematodes, systemic sclerosis, eosinophilic fasciitis, polymyositis, dermatomyositis, polymyalgia rheumatica, vasculitis, temporal arthritis, polyarteritis nodosa, Wegener's granulomatosis, mixed connective tissue diseases and juvenile rheumatoid arthritis), inflammatory disease or symptom of gastrointestinal tract [e.g., Crohn's disease, ulcerative colitis, irritable bowel syndrome (e.g., spastic colon), fibrosis of the liver, inflammation of the oral mucous membrane (e.g., stomatitis and recurrent aphthous stomatitis)], inflammatory disease or symptom of central nervous system (e.g., multiple sclerosis, Alzheimer's disease, and ischemia-reperfusion injury relating to ischemic stroke), pulmonary inflammatory disease or symptom (e.g., asthma, adult respiratory distress syndrome, chronic obliterative pulmonary diseases), disease relating to carbohydrate metabolism (e.g., diabetes and complications derived from diabetes (e.g., diabetic neuropathy, diabetic nephropathy)) including disease of microvessel and large vessel (e.g., arteriosclerosis, retinopathy, nephropathy, nephrotic syndrome and neuropathy (e.g., multiple neuropathy, mononeuropathy and autonomic neuropathy), foot ulcer, articular problem and increase in infection risk), disease relating to abnormality in the differentiation or function of adipocyte or function of smooth muscle cell (e.g., arteriosclerosis and obesity), vascular disease [e.g., artheromatous atherosclerosis, non-artheromatous atherosclerotic disease, ischemic cardiac diseases including myocardial infarction and peripheral arterial obstruction, Raynaud's disease and Raynaud's phenomenon, thromboangiitis obliterans (Buerger's disease)], chronic arthritis, inflammatory bowel disease, SSAO-mediated complications [e.g., diabetes (e.g., insulin-dependent diabetes (IDDM) and noninsulin-dependent diabetes (NIDDM)) and vascular complications (e.g., heart attack, angina pectoris, apoplexy, amputation, blindness and renal failure)], ophthalmic disease associated with hypoxia or ischemia [e.g., retinopathy of prematurity, proliferative diabetic retinopathy, polypoidal choroidal vasculopathy, retinal angiomatous proliferation, retinal artery occlusion, retinal vein occlusion, Coats' disease, familial exudative vitreoretinopathy, pulseless disease (Takayasu's disease), Eales disease, antiphospholipid antibody syndrome, leukemic retinopathy, blood hyperviscosity syndrome, macroglobulinemia, interferon-associated retinopathy, hypertensive retinopathy, radiation retinopathy, corneal epithelial stem cell deficiency] and cataract, and the like.

[0055] The "prophylaxis or treatment of a vascular adhesion protein-1 (VAP-1) associated disease" means administration of the compound of the present invention having a VAP-1 inhibitory action (i.e., VAP-1 inhibitor) to a subject of administration for the purpose of the treatment (including prophylaxis, amelioration of symptom, reduction of symptom, prevention of progress and cure) of the above-mentioned VAP-1 associated disease.

[0056] The subjects of the administration of the pharmaceutical agent, pharmaceutical composition, VAP-1 inhibitor,

pharmaceutical agent for the prophylaxis or treatment of a VAP-1 associated disease in the present invention (hereinafter these are also collectively referred to as the pharmaceutical agent of the present invention) are various animals (e.g., mammals such as human, mouse, rat, swine, dog, cat, horse, bovine and the like, particularly human) and the like.

[0057] The pharmaceutical agent of the present invention can be administered by any route. The administration route in the present invention includes systemic administration (e.g., oral administration or injection administration), topical administration (e.g., instillation administration, intraocular administration and transdermal administration) and the like. The administration route of the pharmaceutical agent of the present invention can be appropriately determined according to whether the application to a VAP-1 associated disease is prophylactic or therapeutic and the like.

[0058] The pharmaceutical agent of the present invention is preferably administered rapidly after a subject of administration such as a mammal, particularly human, is diagnosed to have a risk of a VAP-1 associated disease (prophylactic treatment), or administered rapidly after the subject of administration shows the onset of a VAP-1 associated disease (therapeutic treatment). The treatment plan can be appropriately determined according to the kind of the active ingredient to be used, dose, administration route, cause and, where necessary, level of awareness of the VAP-1 associated disease and the like.

[0059] As an administration method of the pharmaceutical agent of the present invention, a method known per se for general pharmaceutical agents can be used. The administration route may be an appropriately effective one and one or more routes can be used. Accordingly, the above-mentioned administration routes are mere exemplifications free of any limitation.

[0060] The dose of the pharmaceutical agent of the present invention for a subject of administration such as animal including human, particularly human, is an amount sufficient to provide a desired response in the subject of administration for a reasonable period of time. The dose is appropriately determined according to various factors including the strength of the active ingredient to be used, age, kind, symptom, disease state, body weight and severity of disease of the subject of administration, the route, timing and frequency of the administration and the like. The dose can also be appropriately controlled according to the route, timing and frequency of the administration and the like. Depending on the symptom or disease state, a long-term treatment involving plural times of administration may be necessary.

[0061] The dose and administration schedule can be determined by a technique within the range known to those of ordinary skill in the art. In general, the treatment or prophylaxis is started from a dose lower than the optimal dose of the compound. Thereafter, the dose is gradually increased until the optimal effect is obtained under the circumstances. The pharmaceutical agent of the present invention (VAP-1 inhibitor and the like) can be administered generally at a dose of about 0.03 ng/kg body weight/day - about 300 mg/kg body weight/day, preferably about 0.003 μg/kg body weight/day - about 10 mg/kg body weight/day, by a single administration or 2 - 4 portions a day or in a sustained manner.

[0062] The pharmaceutical composition of the present invention preferably contains a "pharmaceutically acceptable carrier" and, as an active ingredient, the compound of the present invention (VAP-1 inhibitor) in an amount sufficient for the prophylactic or therapeutic treatment of a VAP-1 associated disease. The carrier may be any which is generally used as a pharmaceutical agent and is not particularly limited except when limited by physicochemical items for consideration (e.g., solubility, and lack of reactivity with the compound) and administration route.

[0063] While the amount of the compound of the present invention in the pharmaceutical agent of the present invention varies depending on the formulation of the composition, it is generally 0.00001 - 10.0 wt%, preferably 0.001 - 5 wt%, more preferably 0.001 - 1 wt%.

[0064] The administration form of the pharmaceutical agent of the present invention is not particularly limited, and can be administered in various forms to achieve the desired VAP-1 inhibitory action. The pharmaceutical agent of the present invention is formulated using the compound of the present invention alone or in a combination with a pharmaceutically acceptable carrier or an additive such as diluent and the like, and orally or parenterally administered. The characteristics and property of the preparation are determined by the solubility and chemical property of the active ingredient, selected administration route and standard pharmaceutical practice. The preparation to be used for oral administration may be a solid dosage forms (e.g., capsule, tablet, powder) or a liquid form (e.g., solution or suspension) and the like. The preparation to be used for parenteral administration may be an injection, drip infusion, and the like, which are in the form of an aseptic solution or suspension. The solid oral preparation can contain a general excipient and the like. The liquid oral preparation can contain various aromatic, colorant, preservative, stabilizer, solubilizer, suspending agent and the like. The parenteral preparation is, for example, an aseptic aqueous or nonaqueous solution or suspension, and can contain particular various preservatives, stabilizer, buffer agent, solubilizer, suspending agent and the like. Where necessary, various isotonicity agents may be added.

[0065] The pharmaceutical agent of the present invention may contain other pharmaceutically active compound as long as it does not inhibit the effect of the invention.

[0066] The pharmaceutical agent of the present invention can be simultaneously administered with other pharmaceutically active compound as long as it does not inhibit the effect of the invention. The "simultaneous administration" means administration of other pharmaceutically active compound before or simultaneous (e.g., in the same or different preparation) or after administration of the pharmaceutical agent of the present invention. For example, corticosteroid, pred-

nisone, methyl prednisone, dexamethasone or triamcinolone acetonide or noncorticosteroid anti-inflammatory compound (e.g., ibuprofen or flurbiprofen) can be simultaneously administered. Similarly, vitamin and mineral (e.g., zinc, antioxidant (e.g., carotenoid (e.g., xanthophyll carotenoid-like zeaxanthine or lutein))) and micronutrient and the like can be simultaneously administered.

[0067] The compound of the present invention is useful for the production of a pharmaceutical agent such as a VAP-1 inhibitor and a pharmaceutical agent for the prophylaxis or treatment of a VAP-1 associated disease.

[0068] Compound (I) can be produced by the following procedures. However, the procedures are not limited thereto. The procedures can be modified according to a general method known per se.

[0069] Compound (I) can also be represented by the formula:

R^1-NH-X-Y-A-B-D-E

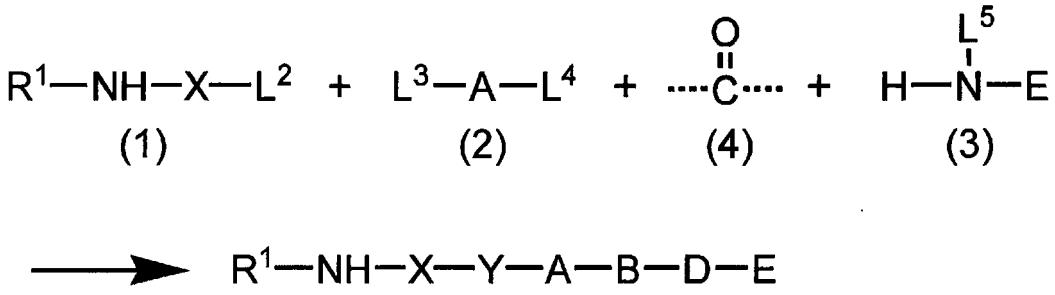
wherein each symbol is as defined above.

[0070] The steps of the production procedure of compound (I) are shown in the following scheme 1.

[0071] Compound (I) can be produced by chemically binding four compounds (1), (2), (3), and carbon monoxide equivalent (4) as partial structures shown in the following scheme 1. Compounds (1), (2), (3) may be in the form of salts.

[0072] The order of binding may be binding (1) and (2) and thereafter (3) via carbon monoxide equivalent (4), or first binding (2) and (3) via carbon monoxide equivalent (4) and finally (1). Compound (I) can be produced by both orders. Where necessary, deprotection of D-E, conversion into a pharmaceutically acceptable salt and the like may be performed. The production method of compound (I) is not limited to have the above, and can appropriately modify the steps according to a general method known per se.

Scheme 1



wherein R^1, X, Y, A, B, D, and E are as defined above. L^2 is a reactive functional group which forms a chemical bond with L^3 of compound (2) to form Y. L^3 is a reactive functional group which forms a chemical bond with L^2 of compound (1) to form Y. L^4 is a functional group that reacts with compound (3) via carbon monoxide equivalent (4) to form B, whereby a carbazic acid ester structure is constructed at the molecule terminal of compound (I). L^5 is hydrogen, lower alkyl, alkoxycarbonyl, acyl or a protecting group.

[0073] L^2 of compound (1) is a reactive functional group which forms a chemical bond with L^3 of compound (2) to form Y. Examples thereof include, but are not limited to, $-(CH_2)_u$-CHO, $-(CH_2)_u$-OH, $-(CH_2)_u$-halogen, $-(CH_2)_u$-COOH, $-(CH_2)_u$-CO-halogen, $-(CH_2)_u$-NH_2, $-(CH_2)_u$-SO_3H, $-(CH_2)_u$-SO_2-halogen, $(CH_2)_u$-O-acyl derived from -$(CH_2)_u$-OH (e.g., $(CH_2)_u$-O-acetyl and the like), -$(CH_2)_u$-sulfonic acid ester (e.g. , -$(CH_2)_u$-OSO_2CH_3 and the like), Wittig reagent derived from -$(CH_2)_u$-halogen and the like, and the like (wherein u is an integer of 0 - 6 and halogen is chlorine, bromine or iodine).

[0074] Compound (1) and a salt thereof may be commercially available, or can also be produced according to the method known per se, which is described in WO 2004/067521, and the like.

[0075] L^3 of compound (2) is a reactive functional group which forms a chemical bond with L^2 of compound (1) to form Y. Examples thereof include, but are not limited to, $-(CH_2)_v$-CHO, -$(CH_2)_v$-OH, -$(CH_2)_v$-halogen, -$(CH_2)_v$-COOH, $(CH_2)_v$-CO-halogen, -$(CH_2)_v$-NH_2, -$(CH_2)_v$-SO_3H, -$(CH_2)_v$-SO_2-halogen, -$(CH_2)_v$-O-acyl derived from -$(CH_2)_v$-OH (e.g. , -$(CH_2)_v$-O-acetyl and the like), -$(CH_2)_v$-sulfonic acid ester (e.g. , -$(CH_2)_v$-OSO_2CH_3 and the like), Wittig reagent derived from -$(CH_2)_v$-halogen and the like, and the like (wherein v is an integer of 0 - 6 and halogen is chlorine, bromine or iodine). L^4 is a functional group that reacts with compound (3) via carbon monoxide equivalent (4) or a compound obtained by previously binding carbon monoxide equivalent (4) to compound (3) to form B, whereby a carbazic acid ester structure is constructed at the molecule terminal of compound (I). Examples thereof include, but are not particularly limited to, -$(CH_2)_w$-OH (wherein w is an integer of 0 - 6 and R^2 is as defined above) .

[0076] Compound (2) and a salt thereof may be commercially available, or can also be produced according to the method known per se, which is described in WO 2004/067521, WO 2006/011631 and the like.

[0077] Compound (3) is a hydrazine equivalent for constructing a carbazic acid ester structure at the molecule terminal of compound (I), and may be commercially available or can be produced according to a method known per se. The protecting group of L^5 is a functional group introduced to avoid unnecessary reactions and removed in an appropriate step. Examples thereof include protecting groups of $(CH_3)_3C$-OCO- shown in the Production Examples and the like. Examples of the lower alkyl, alkoxycarbonyl and acyl for L^5 are those similar to the lower alkyl, alkoxycarbonyl and acyl for the aforementioned R^3.

[0078] (4) is a synthetic equivalent (synthon) of carbon monoxide providing a carbonyl group to B, and may be commercially available, or can be produced according to a method known per se. Specifically, 1,1'-carbonyldiimidazole, chloroformic acid esters, phosgene, bis(trichloromethyl)carbonate [triphosgene] and the like can be used nonlimitatively.

[0079] When compound (I) wherein Y is carbon chain is produced, compound (1) or a salt thereof is chemically bonded to compound (2) or a salt thereof (or compound obtained by condensation of compound (2) and (3) in advance via carbon monoxide equivalent (4)) utilizing Wittig reaction, Horner-Emmons reaction, aldol condensation reaction, Claisen condensation, or a similar carbon-carbon binding formation reaction to construct Y containing lower alkenylene or lower alkynylene. Appropriate salts of compound (1) and (2) may be the same as those exemplified with regard to compound (I). While various carbon-carbon bond forming reactions are utilizable, when Wittig reaction or a similar reaction is utilized, a desirable example includes - $(CH_2)_u$-CHO for L^2 and a phosphonium salt (Wittig reagent) derived from -$(CH_2)_v$-halogen etc. for L^3, or a phosphonium salt (Wittig reagent) derived from -$(CH_2)_u$-halogen etc. for L^2 and -$(CH_2)_v$-CHO for L^3 (wherein u and v are as defined above, and halogen is chlorine, bromine or iodine). The reaction is generally performed in a general solvent such as N,N-dimethylformamide, dimethyl sulfoxide, tetrahydrofuran and dichloromethane, or other organic solvent that does not adversely influence the reaction, or a mixture thereof, in the presence of a general base such as potassium tert-butoxide, sodium hydride, sodium hydroxide and the like. The reaction temperature is not particularly important, and the reaction is performed under cooling or under heating. The resultant product is isolated or purified by a known separation or purification means, concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transition, chromatography and the like, or can also be converted to a salt similar to those exemplified for compound (I).

[0080] Where necessary, lower alkenylene or lower alkynylene is hydrogenated for conversion to lower alkylene. When Y is converted to an alkylene bond, a hydrogenation reaction is performed in the presence of various homogeneous catalysts or heterogeneous catalyst according to a general method. Particularly, catalytic hydrogenation using a heterogeneous catalyst is preferable, which is performed in the presence of a catalyst such as palladium carbon or Raney-nickel.

[0081] When compound (I) wherein Y is ester, amide or sulfonamide is produced, compound (1) or a salt thereof is condensed with compound (2) or a salt thereof (or compound obtained by condensation of compound (2) and (3) in advance via carbon monoxide equivalent (4)) to construct ester or amide bond. In this case, L^2 is - $(CH_2)_u$-OH, - $(CH_z)_u$-NH_2, - $(CH_2)_u$-halogen and the like and L^3 is - $(CH_2)_v$-COOH, - $(CH_2)_v$-CO-halogen, -$(CH_2)_v$-SO_3H, -$(CH_2)_v$-SO_2-halogen and the like, or L^2 is -$(CH_2)_u$-COOH, -$(CH_2)_u$-CO-halogen, -$(CH_2)_u$-SO_3H, -$(CH_2)_u$-SO_2-halogen and the like and L^3 is -$(CH_2)_v$-OH, -$(CH_2)_v$-NH_2, -$(CH_2)_v$-halogen and the like, and Y can be constructed based on a general organic synthesis method (wherein u and v are as defined above, and halogen is chlorine, bromine or iodine). The reaction is generally performed in a general solvent such as dichloromethane, acetone, tetrahydrofuran, diethyl ether and N,N-dimethylformamide, and any other organic solvent that does not adversely influence the reaction, or a mixture thereof. Where necessary, a condensation agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, N,N'-dicyclohexylcarbodiimide, 1,1'-carbonyldiimidazole and the like is used. The reaction is also performed in the presence of an additive such as N,N-dimethyl-4-aminopyridine, 1-hydroxybenzotriazole, 1-hydroxysuccinimido and 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine. The reaction temperature is not particularly important, and the reaction is performed under cooling or under heating.

[0082] When compound (I) wherein Y is a group containing amine is produced, L^2 is - $(CH_2)_u$-NH_2, or a salt thereof and the like and L^3 is --$(CH_2)_v$-CHO, -$(CH_2)_v$-halogen and the like, or L^2 is - $(CH_2)_u$-CHO, -$(CH_2)_u$-halogen and the like and L^3 is -$(CH_2)_v$-NH_2, or a salt thereof and the like, and Y can be constructed based on a general organic synthesis method (wherein u and v are as defined above, and halogen is chlorine, bromine or iodine). Generally, amine and aldehyde is condensed to give a Schiff base, which is reduced by sodium borohydride, sodium cyanoborohydride and the like in a general solvent such as tetrahydrofuran, diethyl ether, alcohol and the like, or any other organic solvent that does not adversely influence the reaction, or a mixture thereof as a reaction solvent, whereby a secondary amine structure is constructed. The same structure is also constructed condensation reaction of amine and a halogen compound. When a halogen compound is utilized, a base such as N,N-diisopropylamine, triethylamine, potassium carbonate and the like is used as a reaction agent, a general solvent such as tetrahydrofuran, acetonitrile and N,N-dimethylformamide, or other organic solvent that does not adversely influence the reaction, or a mixture thereof is used as a reaction solvent. The reaction temperature is not particularly important, and the reaction is performed under cooling or under heating. The resultant product can also be converted to a salt similar to those exemplified for compound (I) .

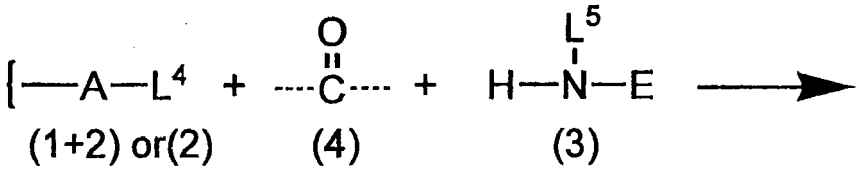
[0083] When compound (I) wherein Y is a group containing an ether bond is produced, L^2 is -$(CH_2)_u$-OH and the like

and L^3 is $-(CH_2)_v$-OH, $-(CH_2)_v$-halogen, $-(CH_2)_v$-sulfonic acid ester and the like, or L^2 is $-(CH_2)_u$-OH, $-(CH_2)_u$-halogen, $-(CH_2)_u$-sulfonic acid ester and the like and L^3 is $-(CH_2)_v$-OH and the like, and Y can be constructed based on a general organic synthesis method (wherein u and v are as defined above, and halogen is chlorine, bromine or iodine). An ether bond can be formed by Williamson method, ether synthesis method from aromatic halide using a copper catalyst and the like, Mitsunobu reaction, other production method known per se. These reactions are generally performed in a general solvent such as acetonitrile, dichloromethane, acetone, tetrahydrofuran and N,N-dimethylformamide, or any other organic solvent that does not adversely influence the reaction, or a mixture thereof. The reaction temperature is not particularly important, and the reaction is performed under cooling or under heating. The resultant product can also be converted to a salt similar to those exemplified for compound (I).

[0084] The molecule terminal of compound (I) is a carbazic acid ester structure.

[0085] One example of the method of introducing a carbazic acid ester structure into the molecule terminal of compound (I) is shown in the following Scheme 2.

Scheme 2



$R^1—NH—X—Y—A—B—D—E$

(wherein R^1, X, Y, A, B, D, and E are as defined for compound (I) and L^4 and L^5 are as defined above.)

[0086] When carbazic acid ester, i.e., compound (I) wherein B is $-(CH_2)_m$-O-CO- is produced, L^4 of compound (2) (or compound obtained by binding compound (1) and (2)) should be a $-(CH_2)_w$-OH structure. It may be incorporated as a hydroxy group into compound (2) in advance as a starting material, or may be constructed as a part of the synthesis step by reduction of the corresponding carboxylic acid, carboxylic acid ester or aldehyde, hydrolysis of halide or ester, hydration of olefin, hydroboration and the like.

[0087] L^4: $-(CH_2)_w$-OH is reacted with, for example, 1,1'-carbonyldiimidazole as a synthetic equivalent of carbon monoxide (4), and then condensed with hydrazine (or protected hydrazine), whereby a carbazic acid ester structure (in the formula (I), B is $-(CH_2)_w$-O-CO-, D is $-NR^3$-, and E is an optionally substituted amino group) can be constructed at the molecule terminal of compound (I), wherein w is as defined above. Alternatively, a carbazic acid ester structure can be constructed at the molecule terminal of compound (I) by reacting hydrazine (or protected hydrazine) and 1H-imidazole-1-carbohydrazide synthesized, for example, from 1,1'-carbonyldiimidazole with L^4: $-(CH_2)_w$-OH, or a metal alcoholate thereof [$-(CH_2)_w$-ONa and the like]. The reaction is generally performed in a general solvent such as tetrahydrofuran, N,N-dimethylformamide, dichloromethane and acetonitrile, or any other organic solvent that does not adversely influence the reaction, or a mixture thereof. Where necessary, deprotection is performed in an appropriate step to give the object compound.

[0088] The thus-produced compound (I) can be isolated or purified by a known separation or purification means such as crystallization, recrystallization, phase transition, chromatography and the like. In addition, it can be converted to a pharmaceutically acceptable salt.

[0089] The present invention is explained in more detail in the following by referring to Examples (Production Examples and Experimental Examples), which are not to be construed as limitative.

Examples

[0090] The starting material compounds used in the following Production Examples can be produced by a known method (WO 2004/067521, WO 2006/011631, WO 2006/028269, WO 2008/066145 etc.) or purchased as commercially available reagents.

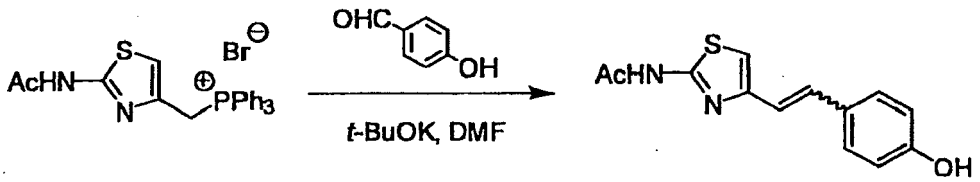
Production Example 1

4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl hydrazinecarboxylate hydrochloride

[0091]

Step 1

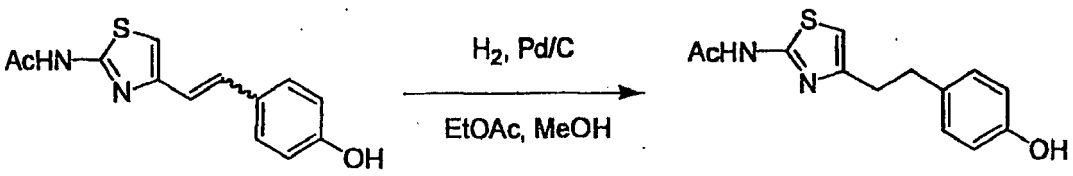
[0092]



[0093] {[2-(Acetylamino)-1,3-thiazol-4-yl]methyl}(triphenyl)phosphoniumbromide (261.1 mg, 0.525 mmol) and 4-hydroxybenzaldehyde (183.2 mg, 1.50 mmol) were dissolved in anhydrous N,N-dimethylformamide (2 ml), and potassium tert-butoxide (56.1 mg, 0.50 mmol) was added at 0°C. After stirring at 90°C for 12 hr, the mixture was cooled to room temperature. Water and ethyl acetate were added, and the mixture was stirred, stood still and then partitioned. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The concentrated residue was purified by silica gel column chromatography (FUJI SILYSIA CHEMICAL LTD. BW-300SP 25 g, ethyl acetate:hexane=4:6→5:5) to give N-{4-[2-(4-hydroxyphenyl)vinyl]-1,3-thiazol-2-yl}acetamide (87.9 mg, 0.338 mmol, yield 67.5%) as a white solid.

Step 2

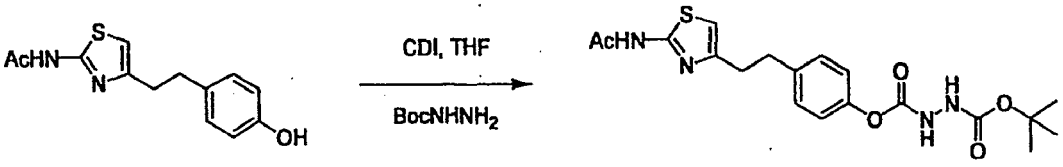
[0094]



[0095] To a solution of N-{4-[2-(4-hydroxyphenyl)vinyl]-1,3-thiazol-2-yl}acetamide (932.3 mg, 3.58 mmol) in ethyl acetate (50 ml) was added 10% palladium carbon, and the mixture was hydrogenated at room temperature and atmospheric pressure. After the completion of the reaction, the reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (FUJI SILYSIA CHEMICAL LTD. BW-300SP 30 g, dichloromethane:methanol=40:1→20:1) to give N-{4-[2-(4-hydroxyphenyl)ethyl]-1,3-thiazol-2-yl}acetamide (771.3 mg, 2.94 mmol, yield 82.1%) as a white solid.

Step 3

[0096]

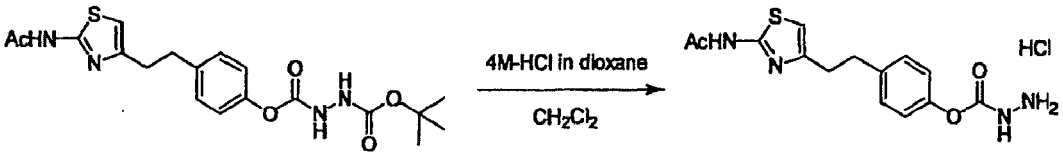


[0097] To a solution of N-{4-[2-(4-hydroxyphenyl)ethyl]-1,3-thiazol-2-yl}acetamide (655.8 mg, 2.50 mmol) in anhydrous tetrahydrofuran (12 ml) was added 1,1'-carbonyldiimidazole (608.1 mg, 3.75 mmol). After stirring at 45°C for 1 hr, the mixture was cooled to room temperature. tert-Butyl carbazate (495.6 mg, 3.75 mmol) was added, and the mixture was

stirred at room temperature for 15 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (FUJI SILYSIA CHEMICAL LTD. BW-300SP 80 g, ethyl acetate:hexane=1:1→3:2) and chemically modified silica gel column chromatography (FUJI SILYSIA CHEMICAL LTD. DM-2035 45 g, dichloromethane:methanol=50:1→20:1) to give 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl tert-butyl hydrazine-1,2-dicarboxylate (526.4 mg, 1.252 mmol, yield 50.0%) as a white solid.

Step 4

[0098]



[0099] To a suspension of 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl tert-butyl hydrazine-1,2-dicarboxylate (445.2 mg, 1.06 mmol) in anhydrous dichloromethane (5.3 ml) was added 4M hydrogen chloride dioxane solution (5.3 ml, 21.3 mmol). After stirring at room temperature for 2 hr, the reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the concentrated residue, and the mixture was concentrated again under reduced pressure. This operation was performed 3 times to remove hydrogen chloride gas azeotropically. The residue was suspended in ethyl acetate, and the solid was collected by filtration, washed twice with ethyl acetate, and dried under reduced pressure to give the title compound (380.5 mg, quantitative) as a white solid. melting point: 167 - 169°C

^{1}H-NMR (200MHz, DMSO-d6): δ(ppm):12.11(1H, brs), 10.97(1H, brs), 7.25(2H, d, J=8.4Hz), 7.06 (2H, d, J=8.4Hz), 6.74(1H, s), 3.05-2.77(4H, m), 2.10(3H, s)

^{13}C-NMR (50MHz, DMSO-d6): δ(ppm):168.5, 157.8, 154.4, 150.1, 148.4, 139.4, 129.6, 121.5, 107.7, 34.0, 32.9, 22.7

MS (ESI$^+$) : 321.1018 [M (free) +H]$^+$

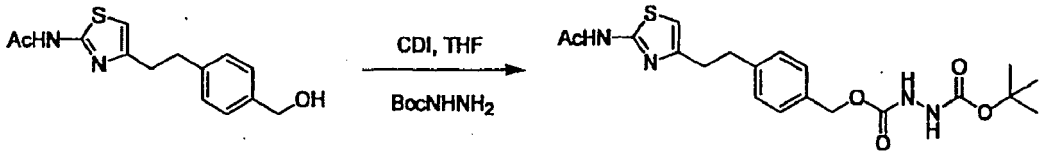
Production Example 2

4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl hydrazinecarboxylate hydrochloride

[0100]

Step 1

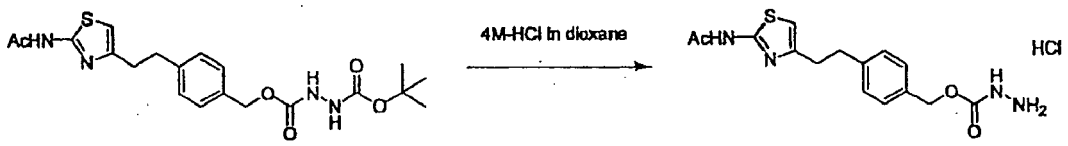
[0101]



[0102] To a suspension of N-(4-{2-[4-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (161.5 mg, 0.584 mmol) in anhydrous tetrahydrofuran (2.4 ml) was added 1,1'-carbonyldiimidazole (142.1 mg, 0.876 mmol), and the mixture was stirred at room temperature for 1.5 hr. tert-Butyl carbazate (115.9 mg, 0.877 mmol) was added, and the mixture was stirred for 16 hr. tert-Butyl carbazate (77.3 mg, 0.584 mmol) was added, and the mixture was stirred for 4 hr. tert-Butyl carbazate (77.3 mg, 0.584 mmol) was added again, and the mixture was stirred for 2 hr. tert-Butyl carbazate (115.9 mg, 0.877 mmol) was added again, and the mixture was stirred for 4 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (FUJI SILYSIA CHEMICAL LTD. BW-300SP 10 g, ethyl acetate:hexane=5:5→6:4→7:3). The residue was further purified by silica gel column chromatography (FUJI SILYSIA CHEMICAL LTD. DM2035 5 g, ethyl acetate:hexane=5:5→1:0) to give 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl tert-butyl hydrazine-1,2-dicarboxylate (207.0 mg, 0.476 mmol, yield 81.6%) as a white solid.

Step 2

[0103]



[0104] To a suspension of 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl tert-butyl hydrazine-1,2-dicarboxylate (203.0 mg, 0.467 mmol) in anhydrous dichloromethane (2.3 ml) was added 4M hydrogen chloride dioxane solution (2.3 ml, 9.2 mmol). After stirring at room temperature for 2.5 hr, the mixture was concentrated under reduced pressure. Ethyl acetate was added to the concentrated residue, and the mixture was concentrated again under reduced pressure. This operation was performed 3 times to remove hydrogen chloride gas azeotropically. The residue was suspended in ethyl acetate and filtered. The filtered product was washed with ethyl acetate and dried under reduced pressure to give the title compound (179.3 mg, quantitative) as a white solid.
melting point 162 - 164°C
^{1}H-NMR (200MHz, DMSO-d6): δ(ppm):12.06(1H, brs), 10.25(3H, br), 7.29(2H, d, J=8.2Hz), 7.20 (2H, d, J=8.2Hz), 6.71 (1H, s), 5.13(2H, s), 3.00-2.78(4H, m), 2.10(3H, s)
^{13}C-NMR (50MHz, DMSO-d6): δ(ppm):168.5, 157.7, 155.8, 150.2, 141.8, 133.5, 128.6, 128.5, 107.7, 67.2, 34.4, 32.8, 22.7 MS(ESI+):357.0965[M(free)+Na]$^+$

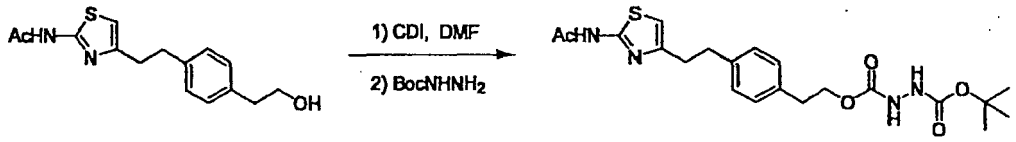
Production Example 3

2-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl hydrazinecarboxylate hydrochloride

[0105]

Step 1

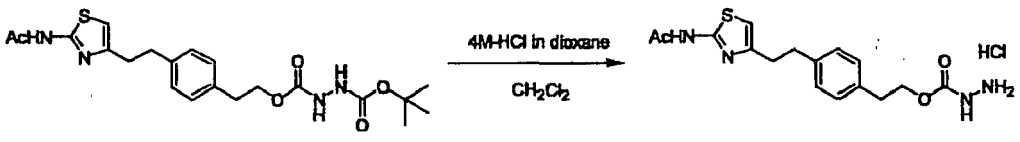
[0106]



[0107] To a suspension of N-(4-{2-[4-(2-hydroxyethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (552.5 mg, 1.799 mmol) in anhydrous tetrahydrofuran (8 ml) was added 1,1'-carbonyldiimidazole (437.8 mg, 2.700 mmol), and the mixture was stirred at 45°C for 0.5 hr. tert-Butyl carbazate (356.8 mg, 2.700 mmol) was added. After stirring for 1 hr, tert-butyl carbazate (356.6 mg, 2.698 mmol) was added. After stirring for 3 hr, tert-butyl carbazate (357.0 mg, 2.701 mmol) was further added. After stirring for 24 hr, the mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (FUJI SILYSIA CHEMICAL LTD. DM1025 60 g, ethyl acetate:hexane=5:5→7:3). The residue was further purified by silica gel column chromatography (Sep pak-5 g, ethyl acetate:hexane=7:3) to give 2-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl tert-butyl hydrazine-1,2-dicarboxylate (755.9 mg, 1.685 mmol, yield 93.6%) as white crystals.

Step 2

[0108]



[0109] To a suspension of 2-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl tert-butyl hydrazine-1,2-dicarboxylate (620.0 mg, 1.382 mmol) in anhydrous dichloromethane (6.9 ml) was added 4M hydrogen chloride dioxane solution (6.9 ml, 27.6 mmol). After stirring at room temperature for 13 hr, the reaction mixture was concentrated under

reduced pressure. Dichloromethane was added to the residue, and the mixture was concentrated again under reduced pressure. The operation was performed twice. Ethyl acetate was further added to the residue, and the mixture was concentrated under reduced pressure. This operation was performed 3 times to remove hydrogen chloride gas azeotropically. The residue was dried under reduced pressure to give a crude product (570.4 mg). The crude product was dissolved in methanol (18 ml) and ethyl acetate (144 ml) was added to recrystallize the crude product. The crystals were collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give the title compound (474.8 mg, 1.234 mmol, yield 89.3%) as a white solid.
melting point 172 - 174°C
^{1}H-NMR (200MHz, DMSO-d6): δ(ppm):12.09(1H, brs), 11.0-9.6(3H, br), 7.25-6.95(4H, m), 6.74(1H, s), 4.27(2H, t, J=6.7Hz), 3.01-2.68(6H, m), 2.11(3H, s)
^{13}C-NMR (50MHz, DMSO-d6): δ(ppm):168.5, 157.8, 155.9, 150.2, 139.7, 135.3, 129.1, 128.5, 107.6, 66.5, 34.3, 32.9, 22.7 MS (ESI+) : 349.1332[M(free)+H]$^+$, 371.1147[M(free)+Na]$^+$

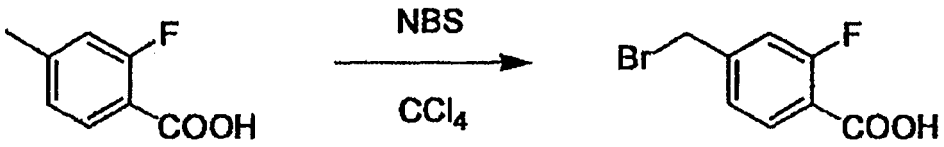
Production Example 4

4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2-fluorobenzyl hydrazinecarboxylate hydrochloride

[0110]

Step 1

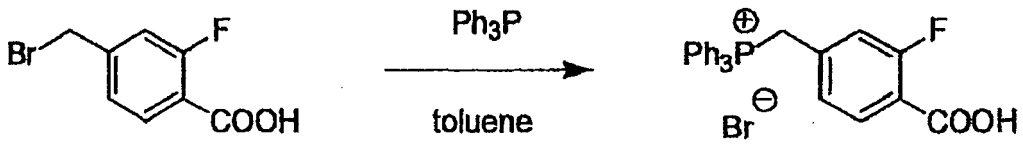
[0111]



[0112] To a solution of 2-fluoro-4-methylbenzoic acid (1.029 g, 6.678 mmol) in carbon tetrachloride (10 ml) were added N-bromosuccinimide (1.189 g, 6.682 mmol) and 2,2'-azobisisobutyronitrile (43.9 mg, 0.267 mmol). After stirring at 90°C for 30 min and at 100°C for 2.5 hr, the mixture was cooled to 0°C. The precipitate was collected by filtration and washed with hexane and water to give a crude product. The crude product was dissolved in ethyl acetate (5 ml), and hexane (10 ml) was added. The precipitated solid was collected by filtration, and dried under reduced pressure to give 4-(bromomethyl)-2-fluorobenzoic acid (838.6 mg, 3.599 mmol, yield 53.9%) as a slightly yellow solid.

Step 2

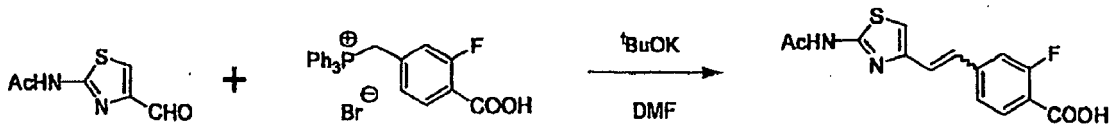
[0113]



[0114] To a suspension of 4-(bromomethyl)-2-fluorobenzoic acid (914.2 mg, 3.923 mmol) in toluene (20 ml) was added triphenylphosphine (1.029 g, 3.923 mmol). After heating the mixture under reflux for 6 hr, the reaction mixture was cooled to room temperature. The precipitate was collected by filtration, and dried under reduced pressure to give (4-carboxy-3-fluorobenzyl)(triphenyl)phosphoniumbromide (2.057 g, quantitative) as a white solid.

Step 3

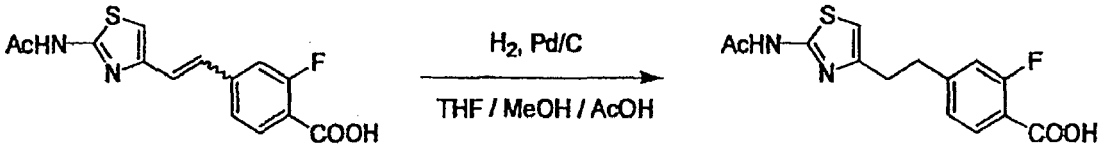
[0115]



[0116] To a solution of (4-carboxy-3-fluorobenzyl)(triphenyl)phosphoniumbromide (2.037g, 4.112 mmol) and N-(4-formyl-1,3-thiazol-2-yl)acetamide (599.5 mg, 3.523 mmol) in anhydrous N,N-dimethylformamide (15 ml) was added potassium tert-butoxide (1.180 g, 10.52 mmol), and the mixture was stirred at room temperature for 3 hr. Water (150 ml) was added to the reaction mixture, and the mixture was washed 3 times with ethyl acetate. While stirring, 1M hydrochloric acid (10.5 ml) was added to the aqueous layer. The precipitated solid was collected by filtration and washed with water. The solid was dried under reduced pressure to give 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]vinyl}-2-fluorobenzoic acid (753.9 mg, 2.461 mmol, yield 69.9%) as a yellow solid.

Step 4

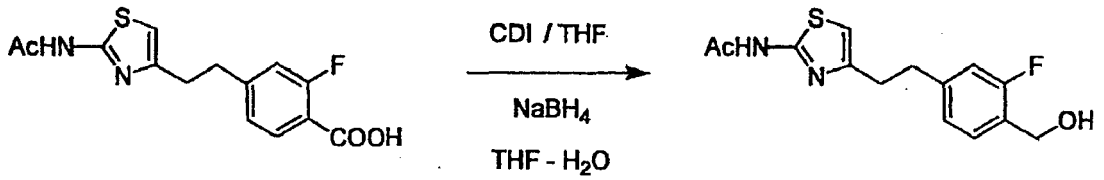
[0117]



[0118] To a mixed solution of 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]vinyl}-2-fluorobenzoic acid (738.9 mg, 2.412 mmol) in tetrahydrofuran (105 ml), methanol (105 ml) and acetic acid (21 ml) was added 10% palladium carbon (593.0 mg, containing 50% water), and the mixture was hydrogenated at room temperature and atmospheric pressure. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The resulting solid was collected by filtration, washed with diisopropyl ether, and dried under reduced pressure to give 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2-fluorobenzoic acid (576.2 mg, 1.869 mmol, yield 77.5%) as a white solid.

Step 5

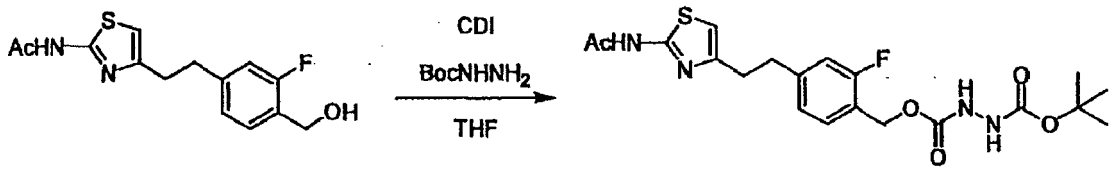
[0119]



[0120] To a suspension of 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2-fluorobenzoic acid (555.0 mg, 1.800 mmol) in anhydrous tetrahydrofuran (4 ml) was added 1,1'-carbonyldiimidazole (364.8 mg, 2.250 mmol), and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was added dropwise to a mixture of sodium borohydride (1.362 g, 36.0 mmol), tetrahydrofuran (36 ml) and water (9 ml), which had been cooled to -25°C. After stirring at not more than 0°C for 1 hr, water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with 1M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, and dried over anhydrous magnesium sulfate. The organic layer was concentrated under reduced pressure, and a mixture of methanol (0.5 ml) and diisopropyl ether (15 ml) was added to the residue. The precipitate was collected by filtration and dried under reduced pressure to give N-(4-{2-[3-fluoro-4-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (342.8 mg, 1.165 mmol, yield 64.7%) as a white solid.

Step 6

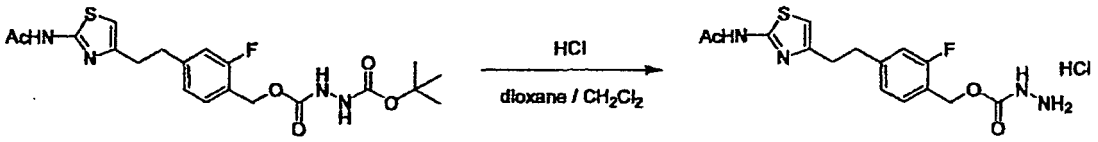
[0121]



[0122] To a suspension of N-(4-{2-[3-fluoro-4-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (118.8 mg, 0.4036 mmol) in anhydrous tetrahydrofuran (1.5 ml) was added 1,1'-carbonyldiimidazole (98.1 mg, 0.605 mmol), and the mixture was stirred at room temperature for 2.5 hr. tert-Butyl carbazate (160.3 mg, 1.213 mmol) was added, and the mixture was stirred at room temperature for 20 hr. Water, 1M hydrochloric acid and ethyl acetate were added, and the mixture was stirred, stood still and then partitioned. The organic layer was washed twice with water, and washed with saturated brine. After drying over anhydrous magnesium sulfate, the residue was concentrated under reduced pressure. The residue was suspended in dichloromethane (15 ml) and filtered. After washing with dichloromethane, the residue was dried under reduced pressure and purified by silica gel column chromatography (FUJI SILYSIA CHEMICAL LTD. BW-300SP 12 g, ethyl acetate:hexane=1:1). The fractions containing the object product were concentrated to give a solid, which was suspended in a mixture of tert-butyl methyl ether (5 ml) and hexane (5 ml) and filtered. The filtered product was dried under reduced pressure to give 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2-fluorobenzyl tert-butyl hydrazine-1,2-dicarboxylate (153.7 mg, 0.340 mmol, yield 84.2%) as a white solid.

Step 7

[0123]



[0124] To a suspension of 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2-fluorobenzyl tert-butyl hydrazine-1,2-dicarboxylate (147.0 mg, 0.325 mmol) in anhydrous dichloromethane (2 ml) was added 4M hydrogen chloride dioxane solution (2 ml). After stirring at room temperature for 2 hr, and the mixture was concentrated under reduced pressure. Ethyl acetate was added to the concentrated residue, and the mixture was concentrated again under reduced pressure. This operation was performed 3 times to remove hydrogen chloride gas azeotropically. The residue was suspended in a mixture of ethanol (2 ml) and ethyl acetate (8 ml) and filtered. The filtered product was washed twice with ethyl acetate, and dried under reduced pressure to give 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2-fluorobenzyl hydrazinecarboxylate hydrochloride (129.1 mg, quantitative) as a white solid.
melting point 162 - 165°C
^{1}H-NMR (400MHz, DMSO-d6): δ (ppm):12.07(1H, brs), 10.5-9.8(2H, br), 10.28(1H, brs), 7.38(1H, t, J=7.9Hz), 7.11(1H, d, J=11.1Hz), 7.06(1H, dd, J=7.9, 1.4Hz), 6.74(1H, s), 5.19(2H, s), 2.99-2.87(4H, m), 2.12(3H, s)
^{13}C-NMR (100MHz, DMSO-d6): δ (ppm) :168.2, 160.3 (d, J=246.9Hz), 157.4, 155.4, 149.7, 145.1(d, J=8.2Hz), 131.0(d, J=4.5Hz), 124.3(d, J=3.0Hz), 119.8(d, J=15.0Hz), 115.1(d, J=21.0Hz), 107.5, 61.2, 33.8, 32.1, 22.4
^{19}F-NMR (376Hz, DMSO-d6): δ (ppm): -120.9
MS(ESI+):353.1037[M(free)+H]$^{+}$, 375.0859[M(free)+Na]$^{+}$

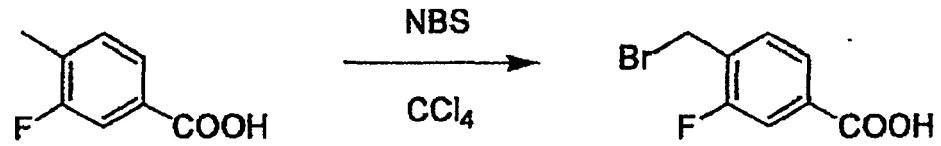
Production Example 5

4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-3-fluorobenzyl hydrazinecarboxylate hydrochloride

[0125]

Step 1

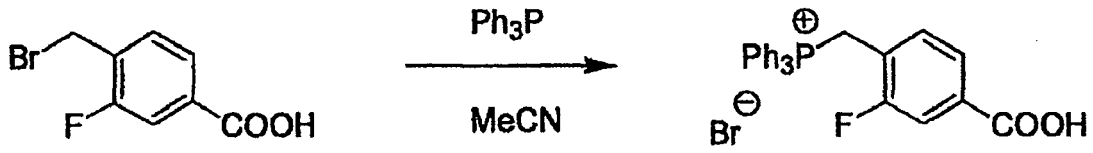
[0126]



[0127] 3-Fluoro-4-methylbenzoic acid (2.541 g, 16.49 mmol) was brominated by a method similar to that of Production Example 4, step 1 to give 4-(bromomethyl)-3-fluorobenzoic acid (2.539 g, 10.90 mmol, yield 66.1%) as a white solid.

Step 2

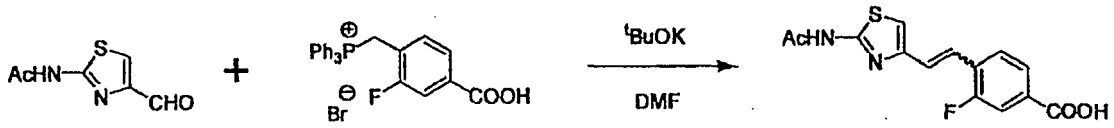
[0128]



[0129] In a similar manner as in Production Example 4, step 2, (4-carboxy-3-fluorobenzyl)(triphenyl)phosphoniumbromide (4.130 g, 8.338 mmol, yield 76.9%) was obtained as a white solid from 4-(bromomethyl)-3-fluorobenzoic acid (2.526 g, 10.84 mmol).

Step 3

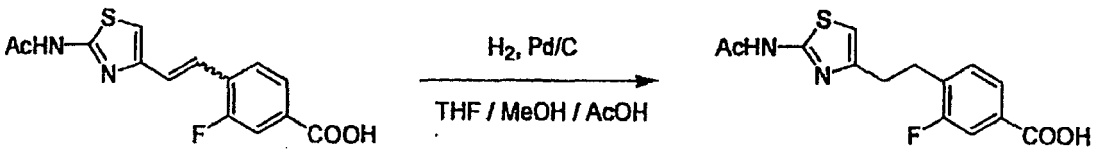
[0130]



[0131] N-(4-Formyl-1,3-thiazol-2-yl)acetamide (941.7 mg, 5.533 mmol) and (4-carboxy-3-fluorobenzyl)(triphenyl)phosphoniumbromide (4.111 g, 8.300 mmol) were condensed by a method similar to that of Production Example 4, step 3, to give 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]vinyl}-3-fluorobenzoic acid (1.086 g, 3.547 mmol, yield 64.1%) as a pale-yellow solid.

Step 4

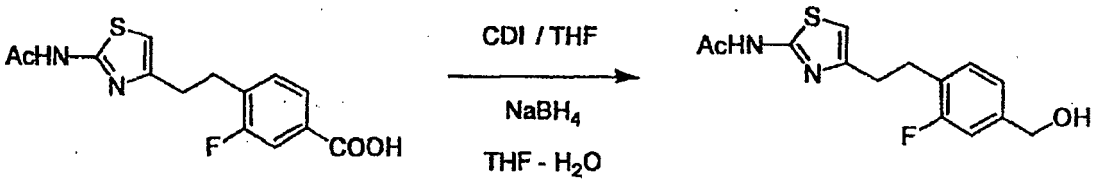
[0132]



[0133] 4-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]vinyl}-3-fluorobenzoic acid (1.000 g, 3.265 mmol) was hydrogenated by a method similar to that of Production Example 4, step 4, to give 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-3-fluorobenzoic acid (620.0 mg, 2.011 mmol, yield 61.7%) as a pale-yellow solid.

Step 5

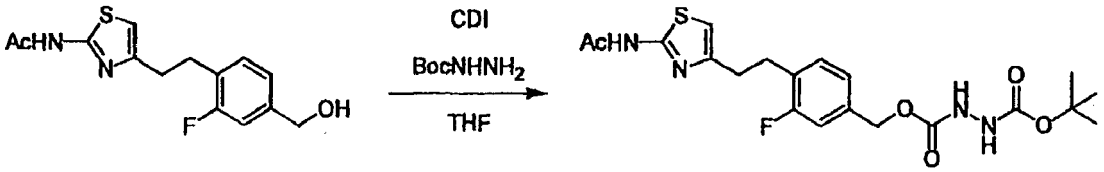
[0134]



[0135] 4-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}-3-fluorobenzoic acid (593.4 mg, 1.924 mmol) was reduced by a method similar to that of Production Example 4, step 5, to give N-(4-{2-[2-fluoro-4-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (406.9 mg, 1.382 mmol, yield 71.8%) as a white solid.

Step 6

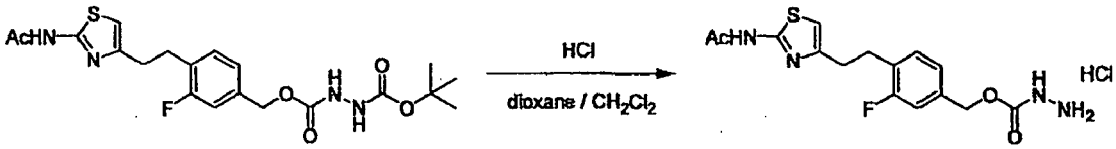
[0136]



[0137] In a similar manner as in Production Example 4, step 6, 4-{2-[2-(acetylamino)-1,3-thiazol-4-y1]ethyl}-3-fluorobenzyl tert-butyl hydrazine-1,2-dicarboxylate (196.0 mg, 0.433 mmol, yield 66.7%) was obtained as a pale-yellow solid from N-(4-{2-[2-fluoro-4-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (191.0 mg, 0.649 mmol).

Step 7

[0138]



[0139] 4-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}-3-fluorobenzyl tert-butyl hydrazine-1,2-dicarboxylate (154.0 mg, 0.341 mmol) was deprotected by a method similar to that of Production Example 4, step 7 to give the title compound (123.0 mg, 0.316 mmol, yield 92.9%) as a white solid.
melting point 204 - 208°C
^{1}H-NMR (400MHz, DMSO-d6): δ (ppm) :12.09(1H, brs), 10.43 (3H, bs), 7.27(1H, t, J=8.0Hz), 7.17(1H, d, J=10.4Hz), 7.14(1H, t, J=8.0Hz), 6.74(1H, s), 5.14(2H, s), 2.97-2.82(4H, m), 2.10(3H, s)
^{13}C-NMR (100MHz, DMSO-d6): δ (ppm):168.4, 160.5(d, J=24.2Hz), 157.7, 149.9, 136.3(d, J=7.4Hz), 131.0, 128.0(d, J=14.9Hz), 124.0, 114.8(d, J=14.9Hz), 107.7, 66.3, 31.5, 27.8, 22.6 MS(ESI+):353.1075[M(free)+H]$^+$, 375.0895[M(free)+Na]$^+$

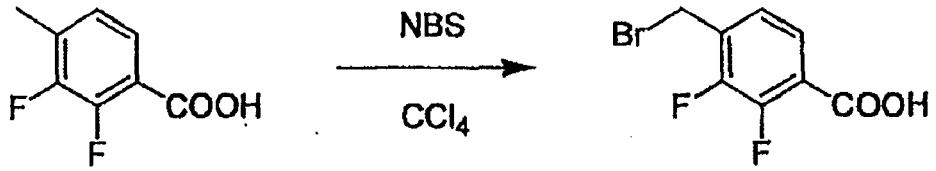
Production Example 6

4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2,3-difluorobenzyl hydrazinecarboxylate hydrochloride

[0140]

Step 1

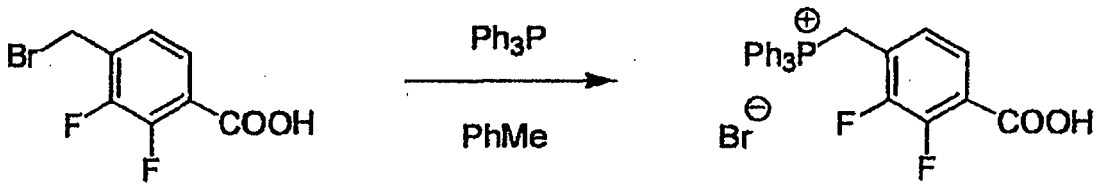
[0141]



[0142] 2,3-Difluoro-4-methylbenzoic acid (4.689 g, 27.24 mmol) was brominated by a method similar to that of Production Example 4, step 1 to give 4-(bromomethyl)-2,3-difluorobenzoic acid (1.724 g, 6.869 mmol, yield 25.2%) as a slightly yellow solid.

Step 2

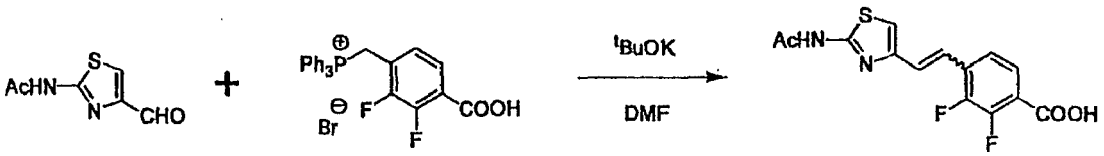
[0143]



[0144] In a similar manner as in Production Example 4, step 2, (4-carboxy-2,3-difluorobenzyl) (triphenyl)phosphoniumbromide (3.246 g, 6.323 mmol, yield 95.2%) was obtained as a white solid from 4-(bromomethyl)-2,3-difluorobenzoic acid (1.667 g, 6.640 mmol).

Step 3

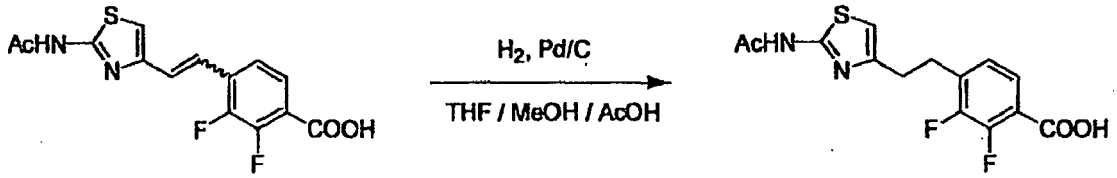
[0145]



[0146] N-(4-Formyl-1,3-thiazol-2-yl)acetamide (1.071 g, 6.292 mmol) and (4-carboxy-2,3-difluorobenzyl)(triphenyl)phosphoniumbromide (3.227 g, 6.287 mmol) were condensed by a method similar to that of Production Example 4, step 3, to give 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]vinyl}-2,3-difluorobenzoic acid (1.550 g, 4.778 mmol, yield 76.0%) as a yellow solid.

Step 4

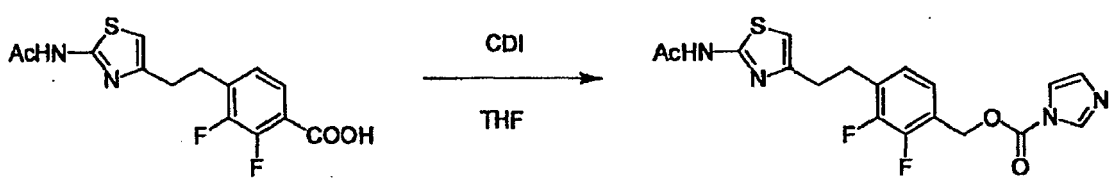
[0147]



[0148] 4-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]vinyl}-2,3-difluorobenzoic acid (1.533 g, 4.728 mmol) was hydrogenated by a method similar to that of Production Example 4, step 4 to give 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2,3-difluorobenzoic acid (1.325 g, 4.059 mmol, yield 85.8%) as a pale-yellow solid.

Step 5

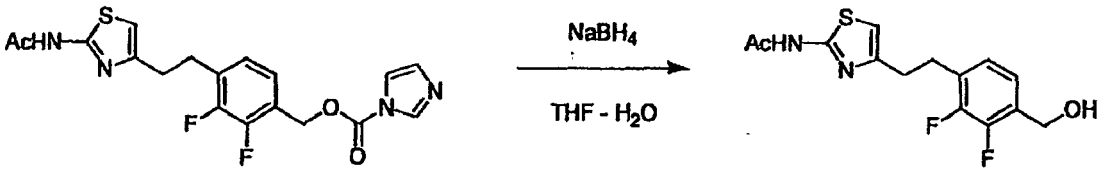
[0149]



[0150] To a suspension of 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2,3-difluorobenzoic acid (654.0 mg, 2.004 mmol) in anhydrous tetrahydrofuran (5 ml) was added 1,1'-carbonyldiimidazole (408.2 mg, 2.517 mmol), and the mixture was stirred at room temperature for 2.5 hr. 1,1'-Carbonyldiimidazole (61.0 mg, 0.376 mmol) was added, and the mixture was stirred at room temperature for 0.5 hr. The reaction mixture was concentrated under reduced pressure, and the precipitate was suspended in ethyl acetate (10 ml) and filtered. The filtered product was dried under reduced pressure to give N-(4-{2-[2,3-difluoro-4-(1H-imidazol-1-ylcarbonyl)phenyl]ethyl)-1,3-thiazol-2-yl)acetamide (516.0 mg, 1.371 mmol, yield 68.4%) as a white solid.

Step 6

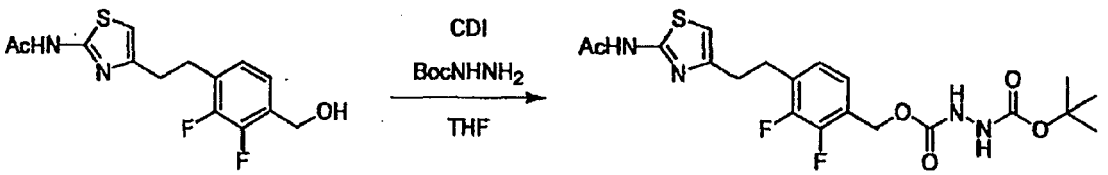
[0151]



[0152] Sodium borohydride (1.009 g, 26.66 mmol) was suspended in a mixture of tetrahydrofuran (36 ml) and water (9 ml), and the suspension was cooled to -20°C. A suspension of N-(4-{2-[2,3-difluoro-4-(1H-imidazol-1-ylcarbonyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (503.5 mg, 1.338 mmol) in anhydrous tetrahydrofuran (4 ml) was added dropwise. After stirring at not more than 0°C for 2.5 hr, saturated aqueous ammonium chloride (50 ml) was added. The mixture was extracted 3 times with ethyl acetate, and the combined organic layer was washed with saturated aqueous ammonium chloride and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the residue were added methanol (0.5 ml) and diisopropyl ether (25 ml), and the mixture was stirred and filtered. The filtered product was dried under reduced pressure to give N-(4-{2-[2,3-difluoro-4-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (316.8 mg, 1.014 mmol, 75.8%) as a white solid.

Step 7

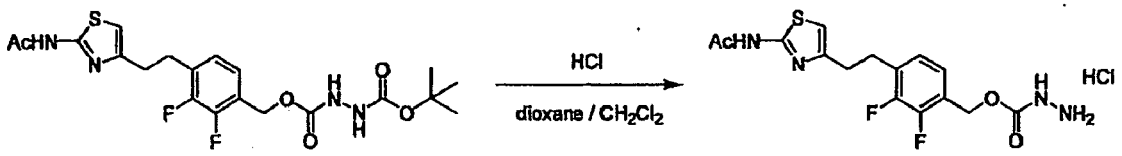
[0153]



[0154] In a similar manner as in Production Example 4, step 6, 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2,3-difluorobenzyl tert-butyl hydrazine-1,2-dicarboxylate (173.4 mg, 0.369 mmol, yield 92.3%) was obtained as a white solid from N-(4-{2-[2,3-difluoro-4-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (125.0 mg, 0.400 mmol).

Step 8

[0155]



[0156] 4-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}-2,3-difluorobenzyl tert-butyl hydrazine-1,2-dicarboxylate (164.8 mg, 0.350 mmol) was deprotected by a method similar to that of Production Example 4, step 7, to give the title compound (145.2 mg, quantitative) as a white solid.
melting point 154 - 160°C
^{1}H-NMR (400MHz, DMSO-d6): δ (ppm):12.10(1H, brs), 10.41(4H, brs), 7.22(1H, t, J=7.3Hz), 7.12(1H, t, J=7.3Hz), 6.76(1H, s), 5.23(2H, s), 3.03-2.87(4H, m), 2.12(3H, s)
^{13}C-NMR (100MHz, DMSO-d6): δ (ppm):168.2, 157.5, 155.2, 149.3, 148.1(dd, J=248.7, 12.6Hz), 147.9(dd, J=244.6, 11.9Hz), 131.0(d, J=12.8Hz), 125.2, 125.1, 122.6(d, J=12.0Hz), 107.7, 60.7, 30.9, 27.5, 22.4
^{19}F-NMR (376Hz, DMSO-d6): δ (ppm) :-144.8 (1F, d, J_{FF}=19.1Hz), - 145.9(1F, d, J_{FF}=19.1Hz)
MS(ESI+):371.0950[M(free)+H]$^+$, 393.0768[M(free)+Na]$^+$

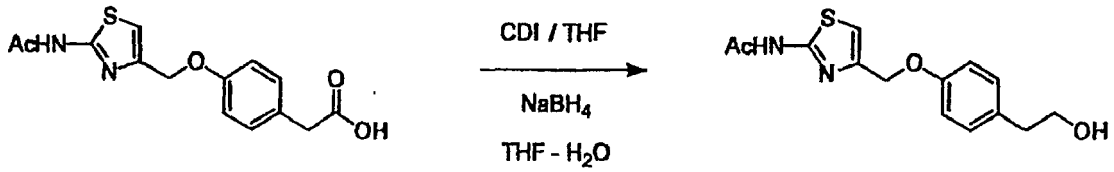
Production Example 7

2-(4-{[2-(acetylamino)-1,3-thiazol-4-yl]methoxy}phenyl)ethyl hydrazinecarboxylate

[0157]

Step 1

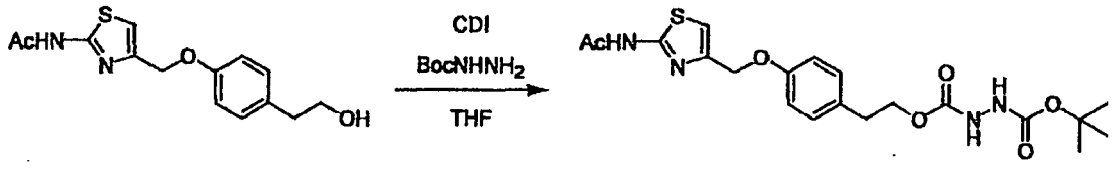
[0158]



[0159] (4-{[2-(Acetylamino)-1,3-thiazol-4-yl]methoxy}phenyl)acetic acid (644.0 mg, 2.102 mmol) was reduced by a method similar to that of Production Example 4, step 5, to give N-(4-{[4-(2-hydroxyethyl)phenoxy]methyl}-1,3-thiazol-2-yl)acetamide (577.6 mg, 1.976 mmol, yield 94.0%) as a white solid.

Step 2

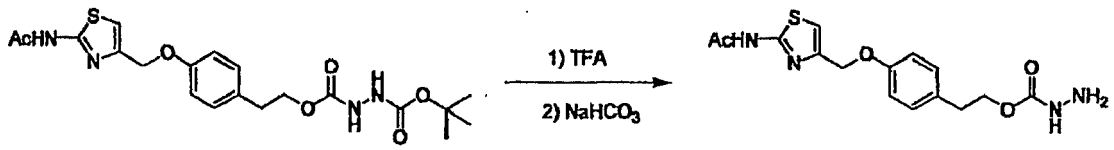
[0160]



[0161] In a similar manner as in Production Example 4, step 6, 2-(4{[2-(acetylamino)-1,3-thiazol-4-yl]methoxy}phenyl)ethyl tert-butyl hydrazine-1,2-dicarboxylate (479.4 mg, quantitative) was obtained as a white solid from N-(4-{[4-(2-hydroxyethyl)phenoxy]methyl}-1,3-thiazol-2-yl)acetamide (250.0 mg, 0.855 mmol).

Step 3

[0162]



[0163] To a solution of 2-(4{[2-(acetylamino)-1,3-thiazol-4-yl]methoxy}phenyl)ethyl tert-butyl hydrazine-1,2-dicarboxylate (0.855 mmol) in dichloromethane (30 ml) was added trifluoroacetic acid (3.18 ml, 42.8 mmol) at 0°C. After stirring at 0°C for 30 min, the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated, aqueous sodium hydrogen carbonate solution was added to the residue, and the mixture was extracted 4 times with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Ethyl acetate (20 ml) was added to suspend the residue. The suspension was filtered and washed once with ethyl acetate and 5 times with diethyl ether, and dried under reduced pressure to give the title compound (105.9 mg, 0.302 mmol, yield 35.3%) as a white solid.
melting point 177 - 180°C
^{1}H-NMR (400MHz, DMSO-d6): δ (ppm):12.13(1H, brs), 8.09(1H, brs), 7.16(1H, s),7.14(2H, d, J=8.6Hz), 6.92(2H, d, J=8.6Hz), 5.00(2H, s), 4.10(2H, t, J=6.9Hz), 3.99(2H, brs), 2.77(2H, t, J=6.9Hz), 2.12(3H, s)
^{13}C-NMR (100MHz, DMSO-d6): δ (ppm):168.6, 158.2, 156,9, 146.6, 130.4, 130.0, 114.8, 111.4, 65.6, 64.9, 34.2, 22.6
MS(ESI+):351.1090[M+H]$^+$, 373.0911[M+Na]$^+$

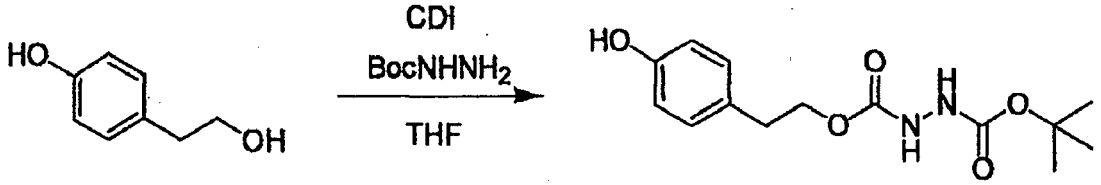
Production Example 8

4-{2-[(hydrazinocarbonyl)oxy]ethyl}phenyl 2-(acetylamino)-1,3-thiazole-4-carboxylate hydrochloride

[0164]

Step 1

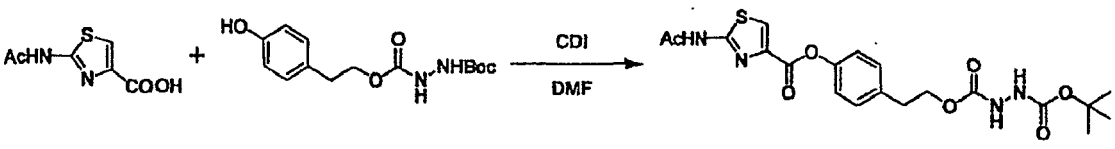
[0165]



[0166] To a suspension of 1,1'-carbonyldiimidazole (1.620 g, 9.989 mmol) in anhydrous tetrahydrofuran (20 ml) was added 2-(4-hydroxyphenyl)ethanol (1.383 g, 10.01 mmol), and the mixture was stirred at room temperature for 3 hr. tert-Butyl carbazate (1.323 g, 10.01 mmol) was added, and the mixture was stirred at room temperature for 1.5 hr. Water (100 ml) and ethyl acetate (100 ml) were added to the reaction mixture, and the mixture was stirred, stood still and then partitioned. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (FUJI SILYSIA CHEMICAL LTD. BW-300SP 40 g, ethyl acetate:hexane=4:6→5:5). The fractions containing the object product were concentrated under reduced pressure, and the obtained solid was suspended in diisopropyl ether (50 ml) and filtered. The filtered product was washed 3 times with diisopropyl ether and dried under reduced pressure to give tert-butyl 2-(4-hydroxyphenyl)ethyl hydrazine-1,2-dicarboxylate (616.7 mg, 2.08 mmol, yield 20.8%) as a white solid.

Step 2

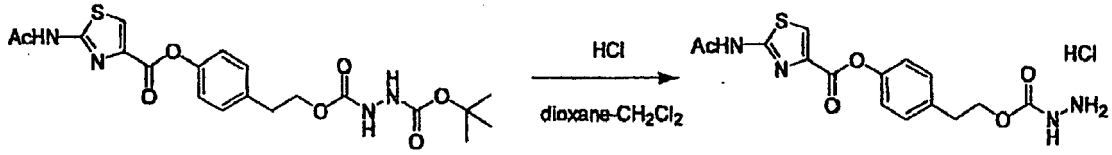
[0167]



[0168] To a suspension of 2-(acetylamino)-1,3-thiazole-4-carboxylic acid (466.2 mg, 2.504 mmol) in anhydrous N,N-dimethylformamide (5 ml) was added 1,1'-carbonyldiimidazole (405.7 mg, 2.502 mmol), and the mixture was stirred at 50°C for 2.5 hr. tert-Butyl 2-(4-hydroxyphenyl)ethyl hydrazine-1,2-dicarboxylate (594.8 mg, 2.001 mmol) was added, and the mixture was stirred at 50°C for 18 hr. Water (40 ml) and ethyl acetate (40 ml) were added to the reaction mixture and the mixture was stirred, stood still and then partitioned. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (FUJI SILYSIA CHEMICAL LTD. BW-300SP 40 g, hexane:ethyl acetate=6:4→5:5). The fractions containing the object product were concentrated under reduced pressure and the obtained solid was suspended in a mixture of hexane (40 ml) and tert-butyl methyl ether (20 ml). The suspension was filtered and dried under reduced pressure to give 2-[4-({[2-(acetylamino)-1,3-thiazol-4-yl]carbonyl}oxy)phenyl]ethyl tert-butyl hydrazine-1,2-dicarboxylate (539.2 mg, 1.161 mmol, yield 58.0%) as a white solid.

Step 3

[0169]



[0170] To a suspension of 2-[4-({[2-(acetylamino)-1,3-thiazol-4-yl]carbonyl}oxy)phenyl]ethyl tert-butyl hydrazine-1,2-dicarboxylate (371.6 mg, 0.800 mmol) in anhydrous dichloromethane (4 ml) was added 4M hydrogen chloride dioxane solution (4 ml). After stirring at room temperature for 2.5 hr, the reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the concentrated residue, and the mixture was concentrated again under reduced pressure. The operation was performed twice to remove hydrogen chloride gas azeotropically. The residue was suspended in a mixture of ethanol (5 ml) and ethyl acetate (30 ml), and the suspension was filtered. The filtered product was washed twice with ethyl acetate and dried under reduced pressure to give the title compound (317.7 mg, 0.793 mmol, yield 99.1%) as a white solid.
melting point 179 - 184°C
^{1}H-NMR (400MHz, DMSO-d6): δ (ppm) :12.55 (1H, brs), 10.09 (4H, br), 8.28(1H, s), 7.35(2H, d, J=8.6Hz), 7.19 (2H, d, J=8.6Hz), 4.35 (2H, t, J=6.6Hz), 2.95 (2H, t, J=6.6Hz), 2.16(3H, s)
^{13}C-NMR (100MHz, DMSO-d6): δ (ppm):169.1, 159.4, 158.2, 155.7, 148.9, 139.7, 135.4, 129.9, 124.4, 121.6, 66.0, 33.7, 22.3 MS(ESI+):387.0729[M(free)+Na]$^+$, 403.0478[M(free)+K]$^+$

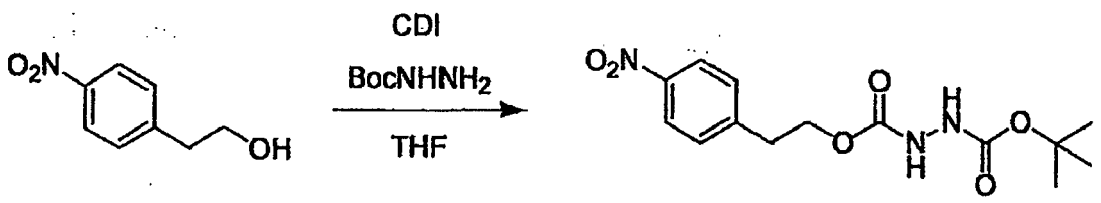
Production Example 9

2-[4-({[2-(acetylamino)-1,3-thiazol-4-yl]carbonyl}amino)phenyl]ethyl hydrazinecarboxylate hydrochloride

[0171]

Step 1

[0172]

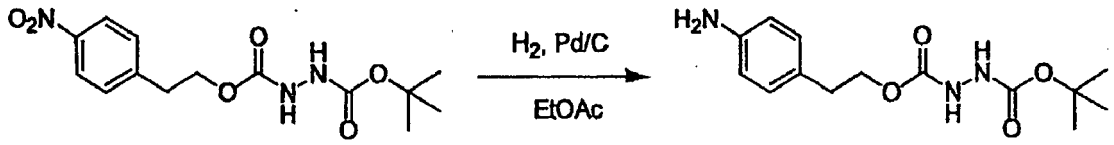


[0173] To a solution of 2-(4-nitrophenyl)ethanol (5.015 g, 30.00 mmol) in anhydrous tetrahydrofuran (50 ml) was added 1,1'-carbonyldiimidazole (5.839 g, 36.01 mmol), and the mixture was stirred at room temperature for 30 min. tert-Butyl carbazate (5.956 g, 45.06 mmol) was added, and the mixture was stirred at room temperature for 16 hr and further at 50°C for 8 hr. 0.5M Hydrochloric acid (100 ml) and ethyl acetate (100 ml) were added to the reaction mixture, and the

mixture was stirred, stood still and then partitioned. The organic layer was washed with 0.5M hydrochloric acid, water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (FUJI SILYSIA CHEMICAL LTD. BW-300SP 200 g, ethyl acetate:hexane=4:6→5:5) to give tert-butyl 2-(4-nitrophenyl)ethyl hydrazine-1,2-dicarboxylate (9.780 g, quantitative) as a slightly yellow solid.

Step 2

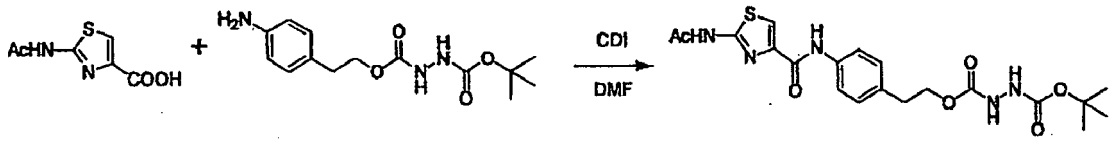
[0174]



[0175] To a solution of tert-butyl 2-(4-nitrophenyl)ethyl hydrazine-1,2-dicarboxylate (9.780 g, 30.00 mmol) in ethyl acetate (100 ml) was added 10% palladium carbon (980.0 mg, containing 50% water), and the mixture was hydrogenated at room temperature and atmospheric pressure. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was suspended in a mixture of hexane (70 ml) and ethyl acetate (30 ml), filtered and dried under reduced pressure to give 2-(4-aminophenyl)ethyl tert-butyl hydrazine-1,2-dicarboxylate (5.207 g, 17.63 mmol, yield 58.8%) as a white solid.

Step 3

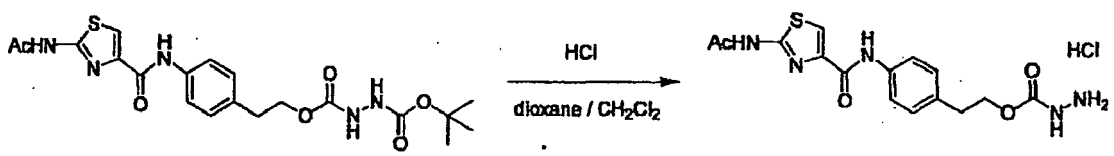
[0176]



[0177] To a suspension of 2-(acetylamino)-1,3-thiazole-4-carboxylic acid (557.3 mg, 2.993 mmol) in anhydrous N,N-dimethylformamide (10 ml) was added 1,1'-carbonyldiimidazole (531.7 mg, 3.279 mmol), and the mixture was stirred at 50°C for 2 hr. 2-(4-Aminophenyl)ethyl tert-butyl hydrazine-1,2-dicarboxylate (1.065 g, 3.607 mmol) was added, and the mixture was stirred at room temperature for 16 hr. Water (100 ml) and ethyl acetate (100 ml) were added to the reaction mixture, and the mixture was stirred, stood still and partitioned. The organic layer was washed with 0.5M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was suspended in tert-butyl methyl ether (30 ml), filtered, washed 3 times with tert-butyl methyl ether, and dried under reduced pressure to give 2-[4-({[2-(acetylamino)-1,3-thiazol-4-yl]carbonyl}amino)phenyl]ethyl tert-butyl hydrazine-1,2-dicarboxylate (1.098 g, 2.368 mmol, yield 79.1%) as a white solid.

Step 4

[0178]



[0179] To a suspension of 2-[4-({[2-(acetylamino)-1,3-thiazol-4-yl]carbonyl}amino)phenyl]ethyl tert-butyl hydrazine-1,2-dicarboxylate (370.8 mg, 0.800 mmol) in anhydrous dichloromethane (4 ml) was added 4M hydrogen chloride dioxane solution (4 ml), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was concentrated under

reduced pressure. Ethyl acetate was added to the concentrated residue, and the mixture was concentrated again under reduced pressure. The operation was performed twice to remove hydrogen chloride gas azeotropically. The residue was suspended in ethyl acetate, filtered, washed 3 times with ethyl acetate and 3 times with methanol, and dried under reduced pressure to give 2-[4-({[2-(acetylamino)-1,3-thiazol-4-yl]carbonyl)amino)phenyl]ethyl hydrazinecarboxylate hydrochloride (280.8 mg, 0.702 mmol, yield 87.8%) as a white solid.

melting point 225 - 233°C

^{1}H-NMR (400MHz, DMSO-d6): δ (ppm):12.33(1H, brs), 10.18(3H, brs), 9.71(1H, brs), 7.94(1H, s), 7.67(2H, d, J=8.5Hz), 7.24(2H, d, J=8.4Hz), 4.30(2H, t, J=6.7Hz), 2.89(2H, t, J=6.6Hz), 2.18 (3H, s)

^{13}C-NMR (100MHz, DMSO-d6): δ (ppm):169.2, 159.3, 158.0, 155.9, 144.5, 136.9, 133.2, 129.3, 120.1, 118.3, 66.3, 34.1, 22.6 MS(ESI+):364.1066[M(free)+H]$^+$, 386.0889[M(free)+Na]$^+$

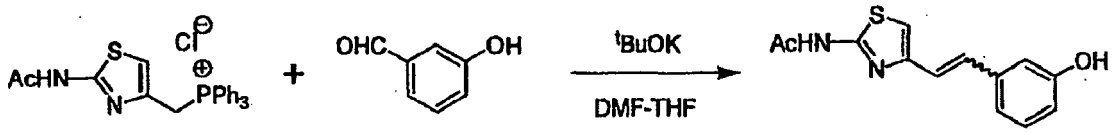
Production Example 10

3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl)phenyl hydrazinecarboxylate hydrochloride

[0180]

Step 1

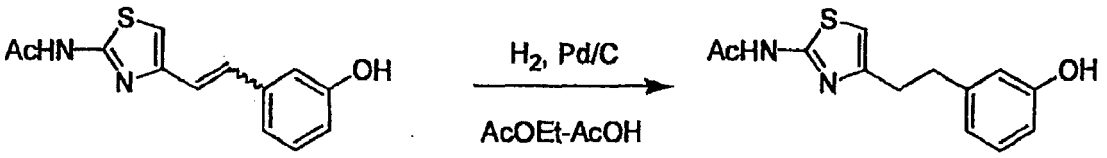
[0181]



[0182] To a solution of {[2-(acetylamino)-1,3-thiazol-4-yl]methyl}(triphenyl)phosphonium chloride (3.894 g, 8.598 mmol) and 3-hydroxybenzaldehyde (1.000 g, 8.189 mmol) in anhydrous N,N-dimethylformamide (42 ml) was added dropwise potassium tert-butoxide tetrahydrofuran solution (1M, 25.4 ml, 25.4 mmol) at 0°C. After stirring at 0°C for 30 min, the mixture was stirred at room temperature for 2 hr. The reaction mixture was cooled to 0°C, and iced water (100 ml) was added. The mixture was washed twice with ethyl acetate, and the aqueous layer was acidified with 1M hydrochloric acid (pH 2.5). The mixture was extracted 3 times with ethyl acetate, and the combined organic layer was washed twice with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (FUJI SILYSIA CHEMICAL LTD. BW-300SP 120 g, ethyl acetate:hexane=1:1) to give N-{3-[2-(4-hydroxyphenyl)vinyl]-1,3-thiazol-2-yl}acetamide (1.953 g, 7.503 mmol, yield 91.6%) as a slightly yellow solid.

Step 2

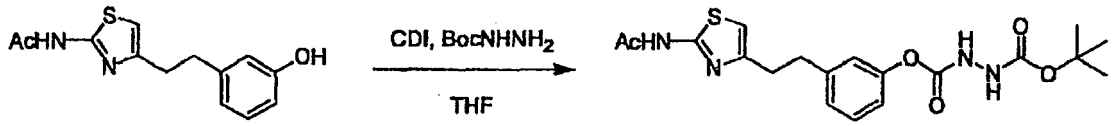
[0183]



[0184] N-{3-[2-(4-Hydroxyphenyl)vinyl]-1,3-thiazol-2-yl}acetamide (1.900 g, 7.299 mmol) was dissolved in a mixture of ethyl acetate (300 ml) and acetic acid (50 ml), and 10% palladium carbon (760 mg, containing 50% water) was added. The mixture was hydrogenated at room temperature under 4 - 5 atm. After the completion of the reaction, the reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate by heating, and recrystallized by cooling to give N-{3-[2-(4-hydroxyphenyl)ethyl]-1,3-thiazol-2-yl}acetamide (1.834 g, 6.993 mmol, yield 95.8%) as a white solid.

Step 3

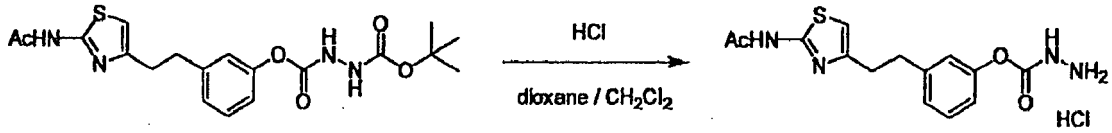
[0185]



[0186] In a similar manner as in Production Example 1, step 3, 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl tert-butyl hydrazine-1,2-dicarboxylate (636.1 mg, 1.513 mmol, yield 52.9%) was obtained as a white solid from N-{3-[2-(4-hydroxyphenyl)ethyl]-1,3-thiazol-2-yl}acetamide (750.0 mg, 2.859 mmol).

Step 4

[0187]



[0188] In a similar manner as in Production Example 1, step 4, 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl tert-butyl hydrazine-1,2-dicarboxylate (260.0 mg, 0.618 mmol) was deprotected to give the title compound (219.0 mg, 0.614 mmol, yield 99.3%) as a white solid.
melting point 158 - 162°C
^{1}H-NMR (400MHz, DMSO-d6): δ (ppm):12.11(1H, brs), 10.99(1H, brs), 11.2-9.8(2H, br), 8.8-7.6(1H, br), 7.32(1H, t, J=7.7Hz), 7.11(1H, d, J=7.4Hz), 7.02-6.97(2H, m), 6.74(1H, s), 2.97-2.86(4H, m), 2.11(3H, s)
^{13}C-NMR (100MHz, DMSO-d6): δ (ppm):168.6, 157.9, 154.3, 150.4, 150.3, 143.8, 129.8, 126.4, 121.6, 119.4, 107.9, 34.5, 32.8, 22.9
MS(ESI+):321.0972[M(free)+H]$^+$, 343.0793[M(free)+Na]$^+$

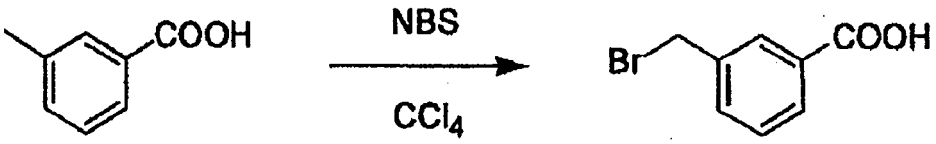
Production Example 11

3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl hydrazinecarboxylate hydrochloride

[0189]

Step 1

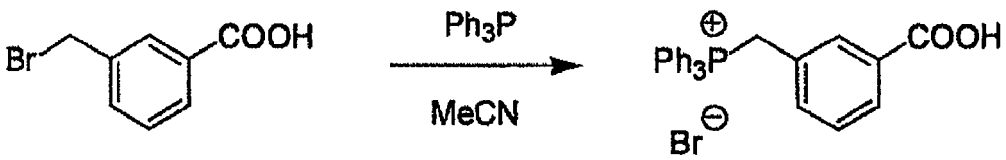
[0190]



[0191] m-Toluic acid (13.62 g, 100.0 mmol) was brominated by a method similar to that of Production Example 4, step 1, to give 3-(bromomethyl)benzoic acid (16.85 g, 78.36 mmol, yield 78.4%) as a pale-yellow solid.

Step 2

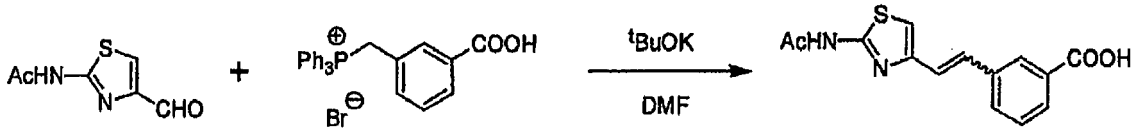
[0192]



[0193] To a solution of 3-(bromomethyl)benzoic acid (16.50 g, 76.73 mmol) in acetonitrile (76.7 ml) was added triphenylphosphine (22.14 g, 84.40 mmol). After heating the mixture under reflux for 2 hr, the reaction mixture was cooled to room temperature. The precipitate was collected by filtration and dried under reduced pressure to give (3-carboxybenzyl)(triphenyl)phosphoniumbromide (30.13 g, 63.12 mmol, yield 82.3%) as a white solid.

Step 3

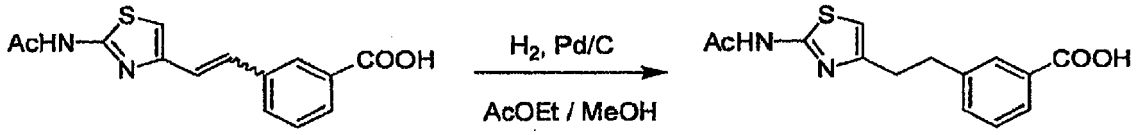
[0194]



[0195] N-(4-Formyl-1,3-thiazol-2-yl)acetamide (1.702 g, 10.00 mmol) and (3-carboxybenzyl)(triphenyl)phosphonium bromide (5.251 g, 11.00 mmol) were condensed by a method similar to that of Production Example 4, step 3, to give 3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]vinyl}benzoic acid (2.862 g, 9.926 mmol, yield 99.3%) as a pale-yellow solid.

Step 4

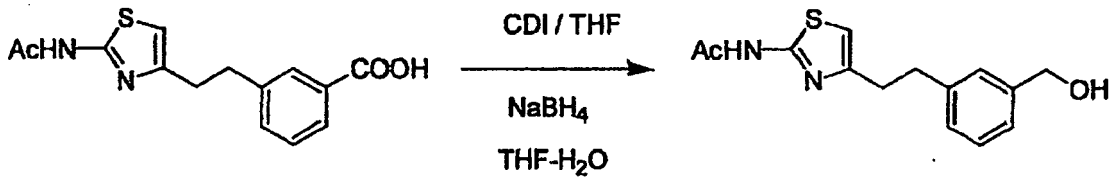
[0196]



[0197] 3-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]vinyl}benzoic acid (1.780 g, 6.174 mmol) was hydrogenated by a method similar to that of Production Example 4, step 4, to give 3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzoic acid (1.323 g, 4.557 mmol, yield 73.8%) as a white solid.

Step 5

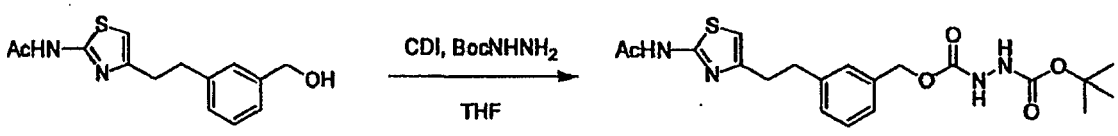
[0198]



[0199] 3-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}benzoic acid (844.6 mg, 2.909 mmol) was reduced by a method similar to that of Production Example 4, step 5, to give N-(4-{2-[3-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (850.0 mg, quantitative) as an off-white solid.

Step 6

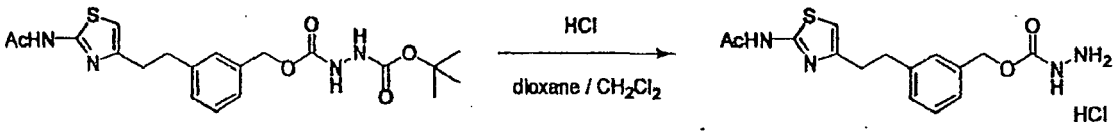
[0200]



[0201] In a similar manner as in Production Example 4, step 6, 3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl tert-butyl hydrazine-1,2-dicarboxylate (710.0 mg, 1.634 mmol, yield 86.2%) was obtained as a white solid from N-(4-{2-[3-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (524.0 mg, 1.896 mmol).

Step 7

[0202]



[0203] In a similar manner as in Production Example 1, step 4, 3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl tert-butyl hydrazine-1,2-dicarboxylate (406.0 mg, 0.934 mmol) was deprotected to give the title compound (329.1 mmol, 0.887 mmol, yield 95.0%) as a white solid.
melting point 113 - 119°C
^{1}H-NMR (400MHz, DMSO-d6): δ (ppm):12.07(1H, brs), 10.37(3H, brs), 7.30-7.16(4H, m), 6.74(1H, s), 5.14(2H, s), 3.55-2.86(4H, m), 2.11 (3H, s)
^{13}C-NMR (100MHz, DMSO-d6): δ (ppm):168.7, 157.9, 156.2, 150.6, 142.2, 136.2, 128.9, 128.7, 128.5, 126.2, 107.9, 67.6, 34.9, 33.2, 22.9
MS (ESI+) : 335.1145 [M (free) +H]$^+$, 357.0957 [M(free)+Na]$^+$

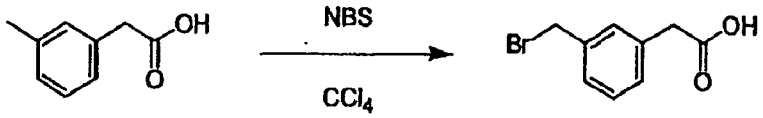
Production Example 12

2-(3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl hydrazinecarboxylate hydrochloride

[0204]

Step 1

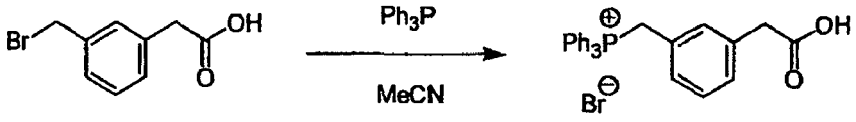
[0205]



[0206] To a solution of m-tolylacetic acid (25.00 g, 166.5 mmol) in anhydrous carbon tetrachloride (200 ml) was added N-bromosuccinimide (30.00 g, 168.6 mmol), and the mixture was gradually heated to the boiling point. After heating the mixture under reflux for 5.5 hr, the reaction mixture was cooled to room temperature, the insoluble material was removed by filtration and washed twice with carbon tetrachloride (100 ml). The filtrate was concentrated, carbon tetrachloride (60 ml) was added and the residue was dissolved by heating at about 70°C. The solution was cooled to about 40°C, and hexane (300 ml) was added dropwise. After stirring at room temperature for 30 min, the precipitated crystals were filtered, washed with hexane and dried under reduced pressure to give (3-bromomethylphenyl)acetic acid (22.80 g, 99.53 mmol, yield 59.8%) as a white solid.

Step 2

[0207]

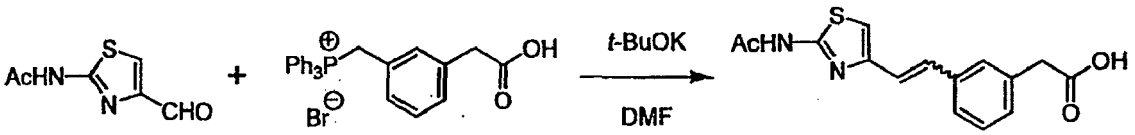


[0208] A solution of (3-bromomethylphenyl)acetic acid (22.00 g, 96.04 mmol) and triphenylphosphine (30.23 g, 115.2

mmol) in anhydrous acetonitrile (300 ml) was heated under reflux for 16 hr. After cooling to room temperature, the solution was concentrated under reduced pressure to about 100 g. Diethyl ether (200 ml) was added, and the mixture was stirred at room temperature for 1 hr. The precipitated crystals were collected by filtration, washed 3 times with diethyl ether and dried under reduced pressure to give [(3-carbonylmethyl)benzyl](triphenyl)phosphonium bromide (43.60 g, 88.73 mmol, yield 92.4%) as a white solid.

Step 3

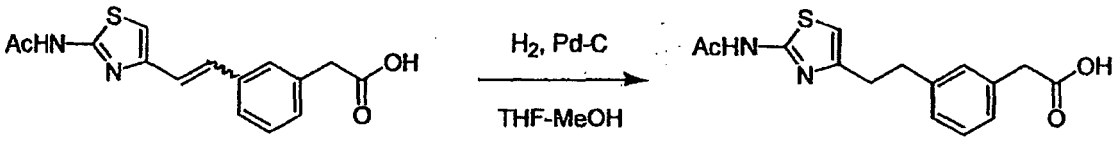
[0209]



[0210] To a suspension of [(3-carbonylmethyl)benzyl](triphenyl)phosphoniumbromide (9.529 g, 19.39 mmol) in anhydrous N,N-dimethylformamide (85 ml) was added potassium tert-butoxide (5.935 g, 52.89 mmol) at 0°C by small portions. After stirring at room temperature for 30 min, (4-formyl-1,3-thiazol-2-yl)acetamide (3.000 g, 17.63 mmol) was added, and the mixture was stirred for 3 hr. After cooling to 0°C, water (200 ml) was added, and the mixture was washed twice with ethyl acetate (100 ml). 6M Hydrochloric acid was added dropwise to the aqueous layer at 0°C to adjust to pH 3, and the mixture was stirred for 30 min. The precipitate was collected by filtration, washed 3 times with water and twice with diisopropyl ether, and dried under reduced pressure to give 3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]vinyl}phenylacetic acid (4.625 g, 15.30 mmol, yield 86.8%) as a white solid.

Step 4

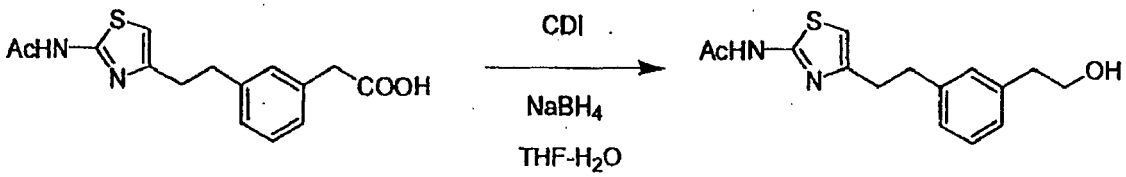
[0211]



[0212] 3-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]vinyl}phenylacetic acid (4.500 g, 14.88 mmol) was dissolved in a mixed solvent of tetrahydrofuran (225 ml) and methanol (90 ml), and 20% palladium carbon (containing 50% water, 1.800 g) was added. Hydrogenation was performed at room temperature - 30°C, 4 atm. After the completion of the reaction, the reaction mixture was filtered through celite, and the filtrate was concentrated. Diethyl ether (100 ml) was added to the residue, and the precipitate was collected by filtration. The filtered product was washed 3 times with diethyl ether, and dried under reduced pressure to give 3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenylacetic acid (4.152 g, 13.64 mmol, yield 91.7%) as a white solid.

Step 5

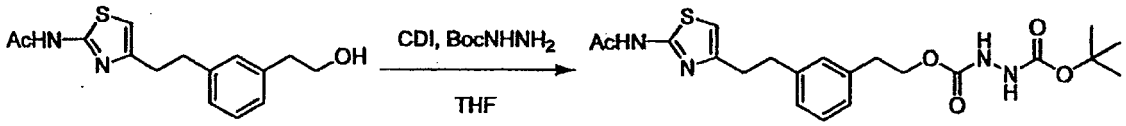
[0213]



[0214] (3-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)acetic acid (935.0 mg, 3.072 mmol) was reduced by a method similar to that of Production Example 4, step 5, to give N-(4-{2-[3-(2-hydroxyethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (670.0 mg, 2.307 mmol, yield 75.1%) as a white solid.

Step 6

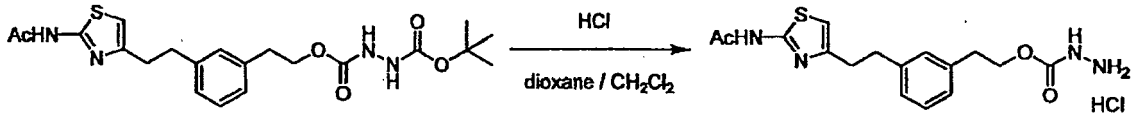
[0215]



[0216] In a similar manner as in Production Example 4, step 6, 2-(3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl tert-butyl hydrazine-1,2-dicarboxylate (534.9 mg, quantitative) was obtained as a white solid from N-(4-{2-[3-(2-hydroxyethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (300.0 mg, 1.033 mmol).

Step 7

[0217]



[0218] 2-(3-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl tert-butyl hydrazine-1,2-dicarboxylate (1.033 mmol) was deprotected by a method similar to that of Production Example 4, step 7, to give the title compound (399.5 mg, quantitative) as a white solid.
melting point 138 - 140°C
^{1}H-NMR (400MHz, DMSO-d6): δ (ppm):12.06(1H, brs), 10.8-9.8(4H, br), 7.20(1H, t, J=7.6Hz), 7.11-7.04(3H, m), 6.73(1H, s), 4.30(2H, t, J=6.9Hz), 2.92-2.85(6H, m), 2.11(3H, s)
^{13}C-NMR (100MHz, DMSO-d6): δ (ppm):168.7, 157.9, 156.2, 150.8, 142.0, 138.0, 129.3, 128.8, 126.9, 107.8, 66.7, 35.0, 34.9, 33.3, 22.9
MS(ESI+):349.1292[M(free)+H]$^+$, 371.1106[M(free)+Na]$^+$

Experimental Example 1

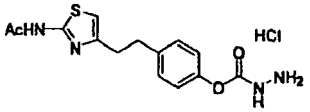
Enzyme activity inhibitory effect on human and rat VAP-1 enzyme (SSAO)

[0219] The compounds of the present invention obtained in Production Examples were examined for the enzyme activity inhibitory effect on human and rat VAP-1 enzyme (SSAO) by the following method.

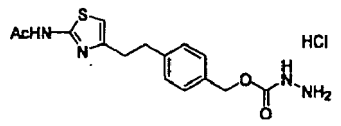
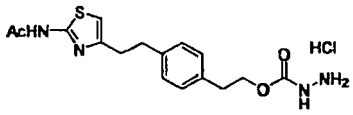
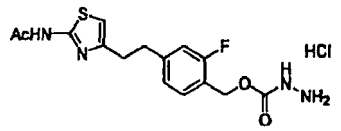
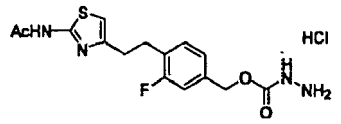
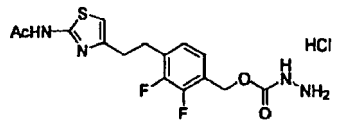
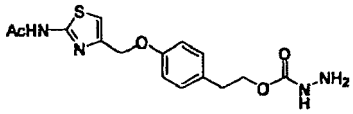
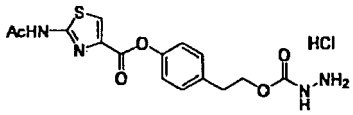
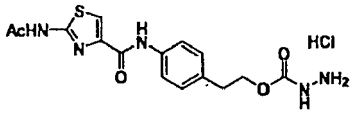
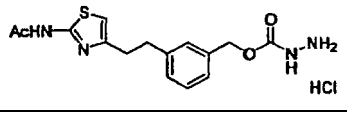
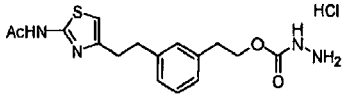
[0220] The VAP-1 enzyme (SSAO) activity in both human and rat was measured by a radiochemical-enzyme assay using ^{14}C-benzylamine as an artificial substrate. Human or rat VAP-1 was cloned from the cDNA library and expressed in a cell. The cell extract was preincubated with a test compound solution (final concentration 1×10^{-7} - 1×10^{-11} mol/l) at room temperature for 20 minutes. Then, ^{14}C-benzylamine (final concentration 1×10^{-5} mol/l) was added, and the mixture was incubated at a final volume of 200 μl at 37°C for 2 hours. The enzyme reaction was stopped by addition of 2 mol/l (200 μl) citric acid. The oxidation product was extracted with 1 ml toluene/ethyl acetate (1:1), and the radioactivity thereof was measured by a liquid scintillation counter. The results are shown in Table 1.

[0221] As shown in Table 1, the compound of the present invention markedly inhibited the enzyme activity of human and rat SSAO.

Table 1: Enzyme activity inhibitory effect on human and rat VAP-1 enzyme (SSAO)

Production Example	Chemical structure	IC_{50} (nM)	
		human	rat
1		2.5	0.2

(continued)

Production Example	Chemical structure	IC_{50} (nM)	
		human	rat
2		0.9	0.7
3		11.7	2.3
4		0.8	0.4
5		1.2	1.1
6		1.3	0.6
7		57.0	7.1
8		6.4	1.7
9		17.1	1.0
11		1.3	0.2
12		3.2	0.5

Experimental Example 2

Enzyme activity inhibitory effect on human monoamine oxidase enzymes (MAO-A and MAO-B)

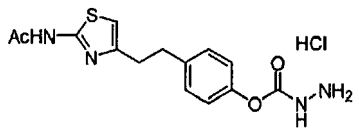
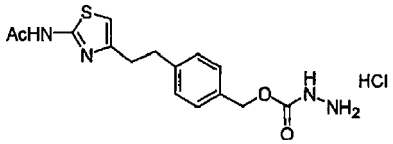
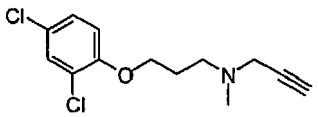
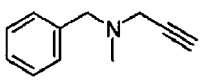
[0222] The compounds of the present invention obtained in Production Examples were examined for the enzyme activity inhibitory effect on human monoamine oxidase enzymes (MAO-A and MAO-B) by the following method.

[0223] Recombinant human MAO-A and MAO-B enzymes were purchased from Sigma Ltd. Human MAO-A and MAO-B activities were measured using MAO Detection Kit (Fluoro MAO, Cell Technology Inc.). The assay was performed

using a 96-well plate. 1×Reactidn buffer (40 μl) was added to each well, and 50 μl of MAO-A or MAO-B was further added. Then, a test compound solution (10 μl, final concentration 1×10^{-5} - 1×10^{-10} mol/l) was added, and the mixture was incubated at 37°C for 20 minutes. The reaction cocktail (100 μl) was added, and the mixture was incubated at a final volume of 200 μl at 37°C for 2 hours. Then, the fluorescence at 590 nm was detected by a multispectro microplate reader (Varioskan, Thermo Fisher Scientific K.K.) using an excitation light at 570 nm. The results are shown in Table 2.

[0224] As shown in Table 2, the compound of the present invention did not show a marked inhibitory action on human MAO-A or MAO-B. Since the compound does not substantially show an inhibitory action on other monoamine oxidases, it is clear that the compound of the present invention shows a selective and specific inhibitory action on SSAO.

Table 2: Enzyme activity inhibitory effect on human monoamine oxidase enzymes (MAO-A and MAO-B)

Compound	Chemical structure	MAO-A inhibition IC_{50} (μM)	MAO-B inhibition IC_{50} (μM)
Production Example 1		>100	>100
Production Example 2		>100	>100
Clorgyline		0.0011	No Data
Pargyline		No data	0.103

INDUSTRIAL APPLICABILITY

[0225] The present invention provides a compound represented by the formula (I)

$$R^1\text{-NH-X-Y-Z} \qquad (I)$$

wherein each symbol is as defined above, useful as a VAP-1 inhibitor, or a pharmaceutically acceptable salt thereof, a pharmaceutical composition, a pharmaceutical agent for the prophylaxis or treatment of VAP-1 associated diseases such as macular edema, vascular hyperpermeable disease, ophthalmic diseases associated with hypoxia or ischemia and cataract and the like, and the like.

Claims

1. A compound represented by the formula (I):

$$R^1\text{-NH-X-Y-Z} \qquad (I)$$

wherein
R^1 is acyl;
X is a divalent residue derived from optionally substituted thiazole;
Y is the formula (III):

$$J\text{-}L\text{-}M \qquad (III)$$

wherein J is a bond, C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene , $-(CH_2)_n$-O-, $-(CH_2)_n$-NH-, $-(CH_2)_n$-CO-

or - $(CH_2)_n$-SO_2-(wherein n is an integer of 0 to 6);
L is a bond, -O-, -NH-, -CO- or -SO_2-;
M is a bond, C_1-C_6 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene, provided that when J is -$(CH_2)_n$-O-, L is not -O-, -NH- and -SO_2-, when J is -$(CH_2)_n$-NH-, L is not -O- and -NH-, when J is -$(CH_2)_n$-CO-, L is not -CO-, when J is -$(CH_2)_n$-SO_2-, L is not -O- and -SO_2- (wherein n is as defied above),
Z is the formula (II):

A-B-D-E (II)

wherein A is a divalent residue derived from optionally substituted benzene;
B is -$(CH_2)_m$-O-CO- wherein m is an integer of 0 to 6;
D is -NR^3- wherein R^3 is hydrogen, C_1-C_6 alkyl, alkoxycarbonyl or acyl; and
E is optionally substituted amino; or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound represented by the aforementioned formula (I) is

4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl hydrazinecarboxylate,
4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl hydrazinecarboxylate,
2-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl hydrazinecarboxylate,
4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2-fluorobenzyl hydrazinecarboxylate,
4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-3-fluorobenzyl hydrazinecarboxylate,
4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}-2,3-difluorobenzyl hydrazinecarboxylate,
2-(4-{[2-(acetylamino)-1,3-thiazol-4-yl]methoxy}phenyl)ethyl hydrazinecarboxylate,
4-{2-[(hydrazinocarbonyl)oxy]ethyl}phenyl 2-(acetylamino)-1,3-thiazole-4-carboxylate,
2-[4-({[2-(acetylamino)-1,3-thiazol-4-yl]carbonyl}amino)phenyl]ethyl hydrazinecarboxylate,
3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl hydrazinecarboxylate,
3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl hydrazinecarboxylate,
2-(3-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl hydrazinecarboxylate,

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein the compound represented by the aforementioned formula (I) is 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl hydrazinecarboxylate or 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl hydrazinecarboxylate, or a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical agent.

5. A pharmaceutical composition comprising the compound of any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof as an active ingredient.

6. The compound of any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof for use as a VAP-1 inhibitor.

7. A pharmaceutical agent for use in the prophylaxis or treatment of VAP-1 associated disease, which agent comprises the compound of any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof as an active ingredient.

8. The pharmaceutical agent for use according to claim 7, wherein the aforementioned VAP-1 associated disease is macular edema (diabetic and nondiabetic macular edema), aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retina edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, ocular inflammatory disease caused by bacterial or viral infection, and by ophthalmic operation, ocular inflammatory disease caused by physical injury to the eye, symptom caused by ocular inflammatory disease including itching, flare, edema and ulcer, erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis (psoriasis, allergic lesion, lichen planus, pityriasis rosea, contact dermatitis, atopic dermatitis, pityriasis rubra pilaris), angioneurotic edema, laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis and laryngitis or otitis

media, cirrhosis, essential stabilized hypertension, diabetes, arteriosclerosis, endothelial injury (in diabetes, arteriosclerosis and hypertension), cardiovascular disease relating to diabetes or uremia, pain relating to gout and arthritis, inflammatory disease or symptom of binding tissue (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and osteoarthritis or degenerative joint disease, Reiter's syndrome, Sjogren's syndrome, Behcet's syndrome, relapsing polychondritis, systemic lupus erythematosus, discoid lupus erythematodes, systemic sclerosis, eosinophilic fasciitis, polymyositis, dermatomyositis, polymyalgia rheumatica, vasculitis, temporal arthritis, polyarteritis nodosa, Wegener's granulomatosis, mixed connective tissue diseases and juvenile rheumatoid arthritis), inflammatory disease or symptom of gastrointestinal tract [Crohn's disease, ulcerative colitis, irritable bowel syndrome (spastic colon), fibrosis of the liver, inflammation of the oral mucous membrane (stomatitis and recurrent aphthous stomatitis)], inflammatory disease or symptom of central nervous system (multiple sclerosis, Alzheimer's disease, and ischemiareperfusion injury relating to ischemic stroke), pulmonary inflammatory disease or symptom (asthma, adult respiratory distress syndrome, chronic obliterative pulmonary diseases), disease relating to carbohydrate metabolism (diabetes and complications derived from diabetes (diabetic neuropathy, diabetic nephropathy)) including disease of microvessel and large vessel (arteriosclerosis, retinopathy, nephropathy, nephrotic syndrome and neuropathy (multiple neuropathy, mononeuropathy and autonomic neuropathy), foot ulcer, articular problem and increase in infection risk), disease relating to abnormality in the differentiation or function of adipocyte or function of smooth muscle cell (arteriosclerosis and obesity), vascular disease [artheromatous atherosclerosis, nonartheromatous atherosclerotic disease, ischemic cardiac diseases including myocardial infarction and peripheral arterial obstruction, Raynaud's disease and Raynaud's phenomenon, thromboangiitis obliterans (Buerger's disease)], chronic arthritis, inflammatory bowel disease, or SSAO-mediated complications [diabetes (insulin-dependent diabetes (IDDM) and noninsulin-dependent diabetes (NIDDM)) and vascular complications (heart attack, angina pectoris, apoplexy, amputation, blindness and renal failure)], ophthalmic disease associated with hypoxia or ischemia [retinopathy of prematurity, proliferative diabetic retinopathy, polypoidal choroidal vasculopathy, retinal angiomatous proliferation, retinal artery occlusion, retinal vein occlusion, Coats' disease, familial exudative vitreoretinopathy, pulseless disease (Takayasu's disease), Eales disease, antiphospholipid antibody syndrome, leukemic retinopathy, blood hyperviscosity syndrome, macroglobulinemia, interferon-associated retinopathy, hypertensive retinopathy, radiation retinopathy, corneal epithelial stem cell deficiency] or cataract.

9. Use of the compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, for the production of a pharmaceutical agent for use as a VAP-1 inhibitor.

10. Use of the compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, for the production of a pharmaceutical agent for the prophylaxis or treatment of a VAP-1 associated disease.

11. Use of claim 10, wherein the aforementioned VAP-1 associated disease is macular edema (diabetic and nondiabetic macular edema), aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retina edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, ocular inflammatory disease caused by bacterial or viral infection, and by ophthalmic operation, ocular inflammatory disease caused by physical injury to the eye, symptom caused by ocular inflammatory disease including itching, flare, edema and ulcer, erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis (psoriasis, allergic lesion, lichen planus, pityriasis rosea, contact dermatitis, atopic dermatitis, pityriasis rubra pilaris), angioneurotic edema, laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis and laryngitis or otitis media, cirrhosis, essential stabilized hypertension, diabetes, arteriosclerosis, endothelial injury (in diabetes, arteriosclerosis and hypertension), cardiovascular disease relating to diabetes or uremia, pain relating to gout and arthritis, inflammatory disease or symptom of binding tissue (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and osteoarthritis or degenerative joint disease, Reiter's syndrome, Sjogren's syndrome, Behcet's syndrome, relapsing polychondritis, systemic lupus erythematosus, discoid lupus erythematodes, systemic sclerosis, eosinophilic fasciitis, polymyositis, dermatomyositis, polymyalgia rheumatica, vasculitis, temporal arthritis, polyarteritis nodosa, Wegener's granulomatosis, mixed connective tissue diseases and juvenile rheumatoid arthritis), inflammatory disease or symptom of gastrointestinal tract [Crohn's disease, ulcerative colitis, irritable bowel syndrome (spastic colon), fibrosis of the liver, inflammation of the oral mucous membrane (stomatitis and recurrent aphthous stomatitis)], inflammatory disease or symptom of central nervous system (multiple sclerosis, Alzheimer's disease, and ischemiareperfusion injury relating to ischemic stroke), pulmonary inflammatory disease or symptom (asthma, adult respiratory distress syndrome, chronic obliterative pulmonary diseases), disease relating to carbohydrate metabolism (diabetes and complications derived from dia-

betes (diabetic neuropathy, diabetic nephropathy)) including disease of microvessel and large vessel (arteriosclerosis, retinopathy, nephropathy, nephrotic syndrome and neuropathy (multiple neuropathy, mononeuropathy and autonomic neuropathy), foot ulcer, articular problem and increase in infection risk), disease relating to abnormality in the differentiation or function of adipocyte or function of smooth muscle cell (arteriosclerosis and obesity), vascular disease [artheromatous atherosclerosis, nonartheromatous atherosclerotic disease, ischemic cardiac diseases including myocardial infarction and peripheral arterial obstruction, Raynaud's disease and Raynaud's phenomenon, thromboangiitis obliterans (Buerger's disease)], chronic arthritis, inflammatory bowel disease, or SSAO-mediated complications [diabetes (insulin-dependent diabetes (IDDM) and noninsulin-dependent diabetes (NIDDM)) and vascular complications (heart attack, angina pectoris, apoplexy, amputation, blindness and renal failure)], ophthalmic disease associated with hypoxia or ischemia [retinopathy of prematurity, proliferative diabetic retinopathy, polypoidal choroidal vasculopathy, retinal angiomatous proliferation, retinal artery occlusion, retinal vein occlusion, Coats' disease, familial exudative vitreoretinopathy, pulseless disease (Takayasu's disease), Eales disease, antiphospholipid antibody syndrome, leukemic retinopathy, blood hyperviscosity syndrome, macroglobulinemia, interferon-associated retinopathy, hypertensive retinopathy, radiation retinopathy, corneal epithelial stem cell deficiency] or cataract.

Patentansprüche

1. Verbindung, die durch die Formel (I) dargestellt wird:

$$R^1\text{-NH-X-Y-Z} \qquad \text{(I)},$$

wobei
R^1 Acyl ist;
X ein zweiwertiger Rest ist, der von gegebenenfalls substituiertem Thiazol abgeleitet ist;
Y die Formel (III) ist:

$$\text{J-L-M} \qquad \text{(III)},$$

wobei J eine Bindung, C_1-C_6-Alkylen, C_2-C_6-Alkenylen, C_2-C_6-Alkinylen, $-(CH_2)_n$-O-, $-(CH_2)_n$-NH-, $-(CH_2)_n$-CO- oder $-(CH_2)_n$-SO_2- ist (wobei n eine ganze Zahl von 0 bis 6 ist);
L eine Bindung, -O-, -NH-, -CO- oder $-SO_2$- ist;
M eine Bindung, C_1-C_6-Alkylen, C_2-C_6-Alkenylen oder C_2-C_6-Alkinylen ist, mit der Maßgabe, dass wenn J = $-(CH_2)_n$-O- ist, dann L nicht -O-, -NH- und $-SO_2$- ist, wenn J = $-(CH_2)_n$-NH- ist, dann L nicht -O- und -NH- ist, wenn J = $-(CH_2)_n$-CO- ist, dann L nicht -CO- ist, wenn J = $-(CH_2)_n$-SO_2-ist, dann L nicht -O- und $-SO_2$- ist (wobei n wie oben definiert ist);
Z die Formel (II) ist:

$$\text{A-B-D-E} \qquad \text{(II)},$$

wobei A ein zweiwertiger Rest ist, der von gegebenenfalls substituiertem Benzol abgeleitet ist;
B = $-(CH_2)_m$-O-CO- ist, wobei m eine ganze Zahl von 0 bis 6 ist;
D = $-NR^3$- ist, wobei R^3 Wasserstoff, C_1-C_6-Alkyl, Alkoxycarbonyl oder Acyl ist; und
E gegebenenfalls substituiertes Amino ist;
oder ein pharmazeutisch annehmbares Salz davon.

2. Verbindung gemäß Anspruch 1, wobei es sich bei der durch die oben genannte Formel (I) dargestellten Verbindung um

4-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}phenylhydrazincarboxylat,
4-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}benzylhydrazincarboxylat,
2-(4-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethylhydrazincarboxylat,
4-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}-2-fluorbenzylhydrazincarboxylat,
4-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}-3-fluorbenzylhydrazincarboxylat,
4-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}-2,3-difluorbenzylhydrazincarboxylat,
2-(4-{[2-(Acetylamino)-1,3-thiazol-4-yl]methoxy}phenyl)ethylhydrazincarboxylat,
4-{2-[(Hydrazinocarbonyl)oxy]ethyl}phenyl-2-(acetylamino)-1,3-thiazol-4-carboxylat,

2-[4-({[2-(Acetylamino)-1,3-thiazol-4-yl]carbonyl}amino)phenyl]ethylhydrazincarboxylat,
3-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}phenylhydrazincarboxylat,
3-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}benzylhydrazincarboxylat,
2-(3-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethylhydrazincarboxylat

oder ein pharmazeutisch annehmbares Salz davon handelt.

3. Verbindung gemäß Anspruch 1, wobei es sich bei der durch die oben genannte Formel (I) dargestellten Verbindung um 4-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}phenylhydrazincarboxylat oder 4-{2-[2-(Acetylamino)-1,3-thiazol-4-yl]ethyl}benzylhydrazincarboxylat oder ein pharmazeutisch annehmbares Salz davon handelt.

4. Verbindung gemäß einem der Ansprüche 1 bis 3 oder ein pharmazeutisch annehmbares Salz davon zur Verwendung als pharmazeutisches Mittel.

5. Pharmazeutische Zusammensetzung, die die Verbindung gemäß einem der Ansprüche 1 bis 3 oder ein pharmazeutisch annehmbares Salz davon als Wirkstoff umfasst.

6. Verbindung gemäß einem der Ansprüche 1 bis 3 oder ein pharmazeutisch annehmbares Salz davon zur Verwendung als VAP-1-Inhibitor.

7. Pharmazeutisches Mittel zur Verwendung bei der Prophylaxe oder Behandlung einer mit VAP-1 zusammenhängenden Krankheit, wobei das Mittel die Verbindung gemäß einem der Ansprüche 1 bis 3 oder ein pharmazeutisch annehmbares Salz davon als Wirkstoff umfasst.

8. Pharmazeutisches Mittel zur Verwendung gemäß Anspruch 7, wobei es sich bei der oben genannten, mit VAP-1 zusammenhängenden Krankheit um folgende handelt: Makulaödem (diabetisches und nichtdiabetisches Makulaödem), altersbedingte Makuladegeneration, altersbedingte scheibenförmige Makuladegeneration, zystoides Makulaödem, Lidödem, Netzhautödem, diabetische Retinopathie, Chorioretinopathie, neovaskuläre Makulopathie, neovaskuläres Glaukom, Uveitis, Iritis, retinale Vaskulitis, Endophthalmitis, Panophthalmitis, metastatische Ophthalmie, Choroiditis, retinale Pigmentepithelitis, Konjunktivitis, Zyklitis, Skleritis, Episkleritis, Optikusneuritis, retrobulbäre Optikusneuritis, Keratitis, Blepharitis, exsudative Netzhautablösung, Hornhautulkus, Bindehautulkus, chronische nummuläre Keratitis, Thygeson-Keratitis, progressiver Ulcus Mooren, durch bakterielle oder virale Infektion und durch Augenoperationen verursachte Augenentzündungskrankheit, durch physische Verletzung des Auges verursachte Augenentzündungskrankheit, durch Augenentzündungskrankheit verursachte Symptome, wie Jucken, Rötung, Ödem und Ulkus, Erythem, Erythema exsudativum multiforme, Erythema nodosum, Erythema annulare, Sklerödem, Dermatitis (Psoriasis, allergische Läsion, Lichen planus, Pityriasis rosea, Kontaktdermatitis, atopische Dermatitis, Pityriasis rubra pilaris), angioneurotisches Ödem, Larynxödem, Zungenödem, subglottale Laryngitis, Bronchitis, Rhinitis, Pharyngitis, Sinusitis und Laryngitis oder Mittelohrentzündung, Zirrhose, stabilisierte essentielle Hypertonie, Diabetes, Arteriosklerose, Endothelverletzung (bei Diabetes, Arteriosklerose und Hypertonie), Herz-Kreislauf-Erkrankung im Zusammenhang mit Diabetes oder Urämie, Schmerzen im Zusammenhang mit Gicht und Arthritis, Entzündungskrankheit oder Symptom des Bindegewebes (rheumatoide Arthritis, Spondylitis ankylosans, Psoriasis-Arthritis und Osteoarthritis oder degenerative Gelenkerkrankung, Morbus Reiter, Sjögren-Syndrom, Morbus Behçet, rezidivierende Polychondritis, systemischer Lupus erythematodes, scheibenförmiger Lupus erythematodes, systemische Sklerose, eosinophile Fasziitis, Polymyositis, Dermatomyositis, Polymyalgia rheumatica, Vaskulitis, Arteriitis temporalis, Polyarteriitis nodosa, Wegener-Granulomatose, gemischte Bindegewebskrankheiten und juvenile rheumatoide Arthritis), Entzündungskrankheit oder Symptom des Magen-Darm-Trakts [Morbus Crohn, ulzerative Kolitis, Reizdarmsyndrom (spastisches Kolon), Leberfibrose, Entzündung der Mundschleimhaut (Stomatitis und chronisch rezidivierende Aphthen)], Entzündungskrankheit oder Symptom des Zentralnervensystems (multiple Sklerose, Alzheimer-Krankheit und Ischämie-Reperfusionsschaden im Zusammenhang mit ischämischem Schlaganfall), Entzündungskrankheit oder Symptom der Lunge (Asthma, Atemnot-Syndrom des Erwachsenen, chronisch obstruktive Lungenerkrankung), Erkrankungen im Zusammenhang mit dem Kohlenhydratstoffwechsel (Diabetes und von Diabetes abgeleitete Komplikationen (Diabetes-Neuropathie, Diabetes-Nephropathie)) einschließlich Erkrankungen von Mikrogefäßen und großen Blutgefäßen (Arteriosklerose, Retinopathie, Nephropathie, nephrotisches Syndrom und Neuropathie (multiple Neuropathie, Mononeuropathie und autonome Neuropathie), diabetisches Fußsyndrom, Gelenkprobleme und Erhöhung des Infektionsrisikos), Erkrankungen im Zusammenhang mit Störungen der Differenzierung oder Funktion von Adipocyten oder Funktion von Zellen der glatten Muskulatur (Arteriosklerose und Adipositas), Gefäßerkrankungen [atheromatöse Atherosklerose, nichtatheromatöse atherosklerotische Erkrankung, ischämische Herzerkrankungen einschließlich Myokardinfarkt und periphere arterielle Ver-

schlusskrankheit, Raynaud-Syndrom und Raynaud-Phänomenon, Thromboangiitis obliterans (Buerger-Syndrom)], chronische Arthritis, Reizdarm oder SSAO-vermittelte Komplikationen [Diabetes (insulinabhängiger Diabetes (IDDM) und nichtinsulinabhängiger Diabetes (NIDDM)) und Gefäßkomplikationen (Herzanfall, Angina pectoris, Apoplexie, Amputation, Blindheit und Nierenversagen)], Augenkrankheiten im Zusammenhang mit Hypoxiie oder Ischämie [Frühgeborenen-Retinopathie, proliferative diabetische Retinopathie, polypoidale choroidale Vaskulopathie, retinale angiomatöse Proliferation, arterieller retinaler Gefäßverschluss, venöser retinaler Gefäßverschluss, Morbus Coats, familiäre exsudative Vitreoretinopathie, Aortenbogen-Syndrom (Takayasu-Syndrom), Eales-Krankheit, Antiphospholipid-Antikörper-Syndrom, leukämische Retinopathie, Bluthyperviskositätssyndrom, Makroglobulinämie, Interferon-assoziierte Retinopathie, hypertonische Retinopathie, Strahlungsretinopathie, Stammzellinsuffizienz des Limbus] oder Katarakt.

9. Verwendung der Verbindung gemäß einem der Ansprüche 1 bis 3 oder eines pharmazeutisch annehmbaren Salzes davon zur Herstellung eines pharmazeutischen Mittels zur Verwendung als VAP-1-Inhibitor.

10. Verwendung der Verbindung gemäß einem der Ansprüche 1 bis 3 oder eines pharmazeutisch annehmbaren Salzes davon zur Herstellung eines pharmazeutischen Mittels zur Prophylaxe oder Behandlung einer mit VAP-1 zusammenhängenden Krankheit.

11. Verwendung gemäß Anspruch 10, wobei es sich bei der oben genannten, mit VAP-1 zusammenhängenden Krankheit um folgende handelt: Makulaödem (diabetisches und nichtdiabetisches Makulaödem), altersbedingte Makuladegeneration, altersbedingte scheibenförmige Makuladegeneration, zystoides Makulaödem, Lidödem, Netzhautödem, diabetische Retinopathie, Chorioretinopathie, neovaskuläre Makulopathie, neovaskuläres Glaukom, Uveitis, Iritis, retinale Vaskulitis, Endophthalmitis, Panophthalmitis, metastatische Ophthalmie, Choroiditis, retinale Pigmentepithelitis, Konjunktivitis, Zyklitis, Skleritis, Episkleritis, Optikusneuritis, retrobulbäre Optikusneuritis, Keratitis, Blepharitis, exsudative Netzhautablösung, Hornhautulkus, Bindehautulkus, chronische nummuläre Keratitis, Thygeson-Keratitis, progressiver Ulcus Mooren, durch bakterielle oder virale Infektion und durch Augenoperationen verursachte Augenentzündungskrankheit, durch physische Verletzung des Auges verursachte Augenentzündungskrankheit, durch Augenentzündungskrankheit verursachte Symptome, wie Jucken, Rötung, Ödem und Ulkus, Erythem, Erythema exsudativum multiforme, Erythema nodosum, Erythema annulare, Sklerödem, Dermatitis (Psoriasis, allergische Läsion, Lichen planus, Pityriasis rosea, Kontaktdermatitis, atopische Dermatitis, Pityriasis rubra pilaris), angioneurotisches Ödem, Larynxödem, Zungenödem, subglottale Laryngitis, Bronchitis, Rhinitis, Pharyngitis, Sinusitis und Laryngitis oder Mittelohrentzündung, Zirrhose, stabilisierte essentielle Hypertonie, Diabetes, Arteriosklerose, Endothelverletzung (bei Diabetes, Arteriosklerose und Hypertonie), Herz-Kreislauf-Erkrankung im Zusammenhang mit Diabetes oder Urämie, Schmerzen im Zusammenhang mit Gicht und Arthritis, Entzündungskrankheit oder Symptom des Bindegewebes (rheumatoide Arthritis, Spondylitis ankylosans, Psoriasis-Arthritis und Osteoarthritis oder degenerative Gelenkerkrankung, Morbus Reiter, Sjögren-Syndrom, Morbus Behcet, rezidivierende Polychondritis, systemischer Lupus erythematodes, scheibenförmiger Lupus erythematodes, systemische Sklerose, eosinophile Fasziitis, Polymyositis, Dermatomyositis, Polymyalgia rheumatica, Vaskulitis, Arteriitis temporalis, Polyarteriitis nodosa, Wegener-Granulomatose, gemischte Bindegewebskrankheiten und juvenile rheumatoide Arthritis), Entzündungskrankheit oder Symptom des Magen-Darm-Trakts [Morbus Crohn, ulzerative Kolitis, Reizdarmsyndrom (spastisches Kolon), Leberfibrose, Entzündung der Mundschleimhaut (Stomatitis und chronisch rezidivierende Aphthen)], Entzündungskrankheit oder Symptom des Zentralnervensystems (multiple Sklerose, Alzheimer-Krankheit und Ischämie-Reperfusionsschaden im Zusammenhang mit ischämischem Schlaganfall), Entzündungskrankheit oder Symptom der Lunge (Asthma, Atemnot-Syndrom des Erwachsenen, chronisch obstruktive Lungenerkrankung), Erkrankungen im Zusammenhang mit dem Kohlenhydratstoffwechsel (Diabetes und von Diabetes abgeleitete Komplikationen (Diabetes-Neuropathie, Diabetes-Nephropathie)) einschließlich Erkrankungen von Mikrogefäßen und großen Blutgefäßen (Arteriosklerose, Retinopathie, Nephropathie, nephrotisches Syndrom und Neuropathie (multiple Neuropathie, Mononeuropathie und autonome Neuropathie), diabetisches Fußsyndrom, Gelenkprobleme und Erhöhung des Infektionsrisikos), Erkrankungen im Zusammenhang mit Störungen der Differenzierung oder Funktion von Adipocyten oder Funktion von Zellen der glatten Muskulatur (Arteriosklerose und Adipositas), Gefäßerkrankungen [atheromatöse Atherosklerose, nichtatheromatöse atherosklerotische Erkrankung, ischämische Herzerkrankungen einschließlich Myokardinfarkt und periphere arterielle Verschlusskrankheit, Raynaud-Syndrom und Raynaud-Phänomenon, Thromboangiitis obliterans (Buerger-Syndrom)], chronische Arthritis, Reizdarm oder SSAO-vermittelte Komplikationen [Diabetes (insulinabhängiger Diabetes (IDDM) und nichtinsulinabhängiger Diabetes (NIDDM)) und Gefäßkomplikationen (Herzanfall, Angina pectoris, Apoplexie, Amputation, Blindheit und Nierenversagen)], Augenkrankheiten im Zusammenhang mit Hypoxiie oder Ischämie [Frühgeborenen-Retinopathie, proliferative diabetische Retinopathie, polypoidale choroidale Vaskulopathie, retinale angiomatöse Proliferation, arterieller retinaler Gefäßverschluss, venöser retinaler Gefäßverschluss, Morbus Coats, familiäre exsudative Vitreoretinopa-

thie, Aortenbogen-Syndrom (Takayasu-Syndrom), Eales-Krankheit, Antiphospholipid-Antikörper-Syndrom, leukämische Retinopathie, Bluthyperviskositätssyndrom, Makroglobulinämie, Interferon-assoziierte Retinopathie, hypertonische Retinopathie, Strahlungsretinopathie, Stammzellinsuffizienz des Limbus] oder Katarakt.

Revendications

1. Composé représenté par la formule (I) :

$$R^1\text{-NH-X-Y-Z} \qquad (I)$$

dans laquelle
R^1 représente un groupe acyle ;
X est un résidu divalent dérivé d'un groupe thiazole éventuellement substitué ;
Y est de formule (III) :

$$J\text{-L-M} \qquad (III)$$

dans laquelle J représente une liaison, un groupe alkylène en C_1 à C_6, alcénylène en C_2 à C_6, alcynylène en C_2 à C_6, - $(CH_2)_n$-O-, -$(CH_2)_n$-NH-, -$(CH_2)_n$-CO- ou - $(CH_2)_n$-SO_2- (où n est un nombre entier de 0 à 6) ;
L représente une liaison, -O-, -NH-, -CO- ou -SO_2- ;
M représente une liaison, un groupe alkylène en C_1 à C_6, alcénylène en C_2 à C_6 ou alcynylène en C_2 à C_6, à condition que lorsque J représente un groupe - $(CH_2)_n$-O-, L ne représente pas -O-, -NH- et -SO_2-, lorsque J représente un groupe -$(CH_2)_n$-NH-, L ne représente pas- O- et -NH-, lorsque J représente un groupe - $(CH_2)_n$-CO-, L ne représente pas -CO-, lorsque J représente un groupe - $(CH_2)_n$-SO_2-, L ne représente pas -O- et -SO_2-(où n est tel que défini ci-dessus),
Z est de formule (II) :

$$A\text{-B-D-E} \qquad (II)$$

dans laquelle A est un résidu divalent dérivé d'un groupe benzène éventuellement substitué ;
B représente un groupe -$(CH_2)_m$-O-CO-, où m est un nombre entier de 0 à 6 ;
D représente un groupe -NR^3-, où R^3 représente un atome d'hydrogène, un groupe alkyle en C_1 à C_6, alcoxycarbonyle ou acyle ; et
E représente un groupe amino éventuellement substitué ;
ou un sel pharmaceutiquement acceptable de celui-ci.

2. Composé selon la revendication 1, dans lequel le composé représenté par la formule (I) susmentionnée est

l'hydrazinecarboxylate de 4-{2-[2-(acétylamino)-1,3-thiazol-4-yl]éthyl}phényle,
l'hydrazinecarboxylate de 4-{2-[2-(acétylamino)-1,3-thiazol-4-yl]éthyl}benzyle,
l'hydrazinecarboxylate de 2-(4-{2-[2-(acétylamino)-1,3-thiazol-4-yl]éthyl}phényl)éthyle,
l'hydrazinecarboxylate de 4-{2-[2-(acétylamino)-1,3-thiazol-4-yl]éthyl}-2-fluorobenzyle,
l'hydrazinecarboxylate de 4-{2-[2-(acétylamino)-1,3-thiazol-4-yl]éthyl}-3-fluorobenzyle,
l'hydrazinecarboxylate de 4-{2-[2-(acétylamino)-1,3-thiazol-4-yl]éthyl}-2,3-difluorobenzyle,
l'hydrazinecarboxylate de 2-(4-{[2-(acétylamino)-1,3-thiazol-4-yl]méthoxy}phényl)éthyle,
le 2-(acétylamino)-1,3-thiazole-4-carboxylate de 4-{2-[(hydrazinocarbonyl)oxy]éthyl}phényle,
l'hydrazinecarboxylate de 2-[4-({[2-(acétylamino)-1,3-thiazol-4-yl]carbonyl}amino)phényl]éthyle,
l'hydrazinecarboxylate de 3-{2-[2-(acétylamino)-1,3-thiazol-4-yl]éthyl}phényle,
l'hydrazinecarboxylate de 3-{2-[2-(acétylamino)-1,3-thiazol-4-yl]éthyl}benzyle,
l'hydrazinecarboxylate de 2-(3-{2-[2-(acétylamino)-1,3-thiazol-4-yl]éthyl}phényl)éthyle,

ou un sel pharmaceutiquement acceptable de celui-ci.

3. Composé selon la revendication 1, dans lequel le composé représenté par la formule (I) susmentionnée est l'hydrazinecarboxylate de 4-{2-[2-(acétylamino)-1,3-thiazol-4-yl]éthyl}phényle ou l'hydrazinecarboxylate de 4-{2-[2-(acétylamino)-1,3-thiazol-4-yl]éthyl)benzyle, ou un sel pharmaceutiquement acceptable de celui-ci.

4. Composé selon l'une quelconque des revendications 1 à 3, ou un sel pharmaceutiquement acceptable de celui-ci, pour son utilisation en tant qu'agent pharmaceutique.

5. Composition pharmaceutique comprenant le composé selon l'une quelconque des revendications 1 à 3 ou un sel pharmaceutiquement acceptable de celui-ci en tant que principe actif.

6. Composé selon l'une quelconque des revendications 1 à 3 ou un sel pharmaceutiquement acceptable de celui-ci pour son utilisation en tant qu'inhibiteur de la VAP-1.

7. Agent pharmaceutique pour son utilisation dans la prophylaxie ou le traitement d'une maladie associée à la VAP-1, lequel agent comprend le composé selon l'une quelconque des revendications 1 à 3 ou un sel pharmaceutiquement acceptable de celui-ci en tant que principe actif.

8. Agent pharmaceutique pour son utilisation selon la revendication 7, dans lequel la maladie associée à la VAP-1 susmentionnée est l'oedème maculaire (oedème maculaire diabétique et non diabétique), la dégénérescence maculaire liée à l'âge, la dégénérescence maculaire disciforme liée à l'âge, l'oedème maculaire cystoïde, l'oedème palpébral, l'oedème de la rétine, une rétinopathie diabétique, une choriorétinopathie, une maculopathie néovasculaire, un glaucome néovasculaire, une uvéite, une iritite, une vascularite rétinienne, une endophtalmite, une panophtalmite, une ophtalmie métastasée, une choroïdite, une épithélite pigmentaire rétinienne, une conjonctivite, une cyclite, une sclérite, une épisclérite, une névrite optique, une névrite optique rétrobulbaire, une kératite, une blépharite, un décollement de la rétine exsudatif, un ulcère de la cornée, un ulcère de la conjonctive, une kératite nummulaire chronique, une kératite de Thygeson, un ulcère progressif de Mooren, une maladie oculaire inflammatoire provoquée par une infection bactérienne ou virale, et par une opération ophtalmique, une maladie oculaire inflammatoire provoquée par une lésion physique de l'oedil, un symptôme provoqué par une maladie oculaire inflammatoire y compris des démangeaisons, des éblouissements, un oedème et un ulcère, un érythème, un érythème exsudatif multiforme, un érythème noueux, un érythème annulaire, une sclérodermie, une dermite (psoriasis, lésion allergique, lichen plan, pityriasis rosé, dermite de contact, dermite atopique, pityriasis rubra pilaire), un oedème angioneurotique, un oedème du larynx, un oedème de la glotte, une laryngite sous-glottique, une bronchite, une rhinite, une pharyngite, une sinusite et une laryngite ou une otite moyenne, une cirrhose, une hypertension stabilisée essentielle, le diabète, l'artériosclérose, une lésion endothéliale (dans le diabète, l'artériosclérose et l'hypertension), une maladie cardiovasculaire associée au diabète ou à l'urémie, une douleur associée à la goutte et à l'arthrite, une maladie ou un symptôme inflammatoire du tissu conjonctif (polyarthrite rhumatoïde, spondylarthrite ankylosante, arthrite psoriasique et arthrose ou maladie articulaire dégénérative, syndrome de Reiter, syndrome de Sjögren, syndrome de Behçet, polychondrite récidivante, lupus systémique érythémateux, lupus discoïde érythémateux, sclérose systémique, fasciite à éosinophiles, polymyosite, dermatomyosite, polymyalgie rhumatismale, vascularite, arthrite temporaire, polyartérite noueuse, granulomatose de Wegener, maladies mixtes du tissu conjonctif et polyarthrite rhumatoïde juvénile), une maladie ou un symptôme inflammatoire du tube digestif [maladie de Crohn, colite ulcéreuse, syndrome de l'intestin irritable (côlon spastique), fibrose du foie, inflammation de la muqueuse orale (stomatite et stomatite aphteuse récurrente)], une maladie ou un symptôme inflammatoire du système nerveux central (sclérose en plaques, maladie d'Alzheimer et lésion d'ischémie-reperfusion associée à un accident vasculaire cérébral ischémique), une maladie ou un symptôme inflammatoire du poumon (asthme, syndrome de détresse respiratoire de l'adulte, bronchopneumopathies chroniques obstructives), maladie associée au métabolisme des glucides (diabète et complications dérivées du diabète (neuropathie diabétique, néphropathie diabétique)) y compris une maladie des microvaisseaux et des gros vaisseaux (artériosclérose, rétinopathie, néphropathie, syndrome néphrotique et neuropathie (neuropathie multiple, mononeuropathie et neuropathie autonome), ulcère du pied, problème articulaire et augmentation du risque d'infection), une maladie associée à une anomalie dans la différenciation ou la fonction des adipocytes ou la fonction des cellules des muscles lisses (artériosclérose et obésité), une maladie vasculaire [athérosclérose athéromateuse, maladie athéroscléreuse non athéromateuse, maladies cardiaques ischémiques y compris infarctus du myocarde et obstruction des artères périphériques, maladie de Raynaud et phénomène de Raynaud, thromboangéite oblitérante (maladie de Buerger)], une arthrite chronique, une maladie inflammatoire de l'intestin, ou des complications médiées par la SSAO [diabète (diabète insulinodépendant (DID) et diabète non insulino-dépendant (DNID)] et des complications vasculaires (crise cardiaque, angine de poitrine, apoplexie, amputation, cécité et insuffisance rénale)], une maladie ophtalmique associée à une hypoxie ou à une ischémie [rétinopathie du prématuré, rétinopathie diabétique proliférante, vasculopathie choroïdienne polypoïdale, prolifération angiomateuse rétinienne, occlusion de l'artère rétinienne, occlusion de la veine rétinienne, maladie de Coats, vitréorétinopathie exsudative rétinienne, maladie sans pouls (maladie de Takayasu), maladie de Eales, syndrome des anticorps antiphospholipides, rétinopathie leucémique, syndrome de l'hyperviscosité sanguine, macroglobulinémie, rétinopathie associée aux interférons, rétinopathie hypertensive, rétinopathie due à des radia-

tions, déficience des cellules souches épithéliales de la cornée] ou la cataracte.

9. Utilisation du composé selon l'une quelconque des revendications 1 à 3, ou d'un sel pharmaceutiquement acceptable de celui-ci, pour la production d'un agent pharmaceutique pour son utilisation en tant qu'inhibiteur de la VAP-1.

10. Utilisation du composé selon l'une quelconque des revendications 1 à 3, ou d'un sel pharmaceutiquement acceptable de celui-ci, pour la production d'un agent pharmaceutique destiné à la prophylaxie ou au traitement d'une maladie associée à la VAP-1.

11. Utilisation selon la revendication 10, dans laquelle la maladie associée à la VAP-1 susmentionnée est l'oedème maculaire (oedème maculaire diabétique et non diabétique), la dégénérescence maculaire liée à l'âge, la dégénérescence maculaire disciforme liée à l'âge, l'oedème maculaire cystoïde, l'oedème palpébral, l'oedème de la rétine, une rétinopathie diabétique, une choriorétinopathie, une maculopathie néovasculaire, un glaucome néovasculaire, une uvéite, une iritite, une vascularite rétinienne, une endophtalmite, une panophtalmite, une ophtalmie métastasée, une choroïdite, une épithélite pigmentaire rétinienne, une conjonctivite, une cyclite, une sclérite, une épisclérite, une névrite optique, une névrite optique rétrobulbaire, une kératite, une blépharite, un décollement de la rétine exsudatif, un ulcère de la cornée, un ulcère de la conjonctive, une kératite nummulaire chronique, une kératite de Thygeson, un ulcère progressif de Mooren, une maladie oculaire inflammatoire provoquée par une infection bactérienne ou virale, et par une opération ophtalmique, une maladie oculaire inflammatoire provoquée par une lésion physique de l'oedil, un symptôme provoqué par une maladie oculaire inflammatoire y compris des démangeaisons, des éblouissements, un oedème et un ulcère, un érythème, un érythème exsudatif multiforme, un érythème noueux, un érythème annulaire, une sclérodermie, une dermite (psoriasis, lésion allergique, lichen plan, pityriasis rosé, dermite de contact, dermite atopique, pityriasis rubra pilaire), un oedème angioneurotique, un oedème du larynx, un oedème de la glotte, une laryngite sous-glottique, une bronchite, une rhinite, une pharyngite, une sinusite et une laryngite ou une otite moyenne, une cirrhose, une hyper-tension stabilisée essentielle, le diabète, l'artériosclérose, une lésion endothéliale (dans le diabète, l'artériosclérose et l'hypertension), une maladie cardiovasculaire associée au diabète ou à l'urémie, une douleur associée à la goutte et à l'arthrite, une maladie ou un symptôme inflammatoire du tissu conjonctif (polyarthrite rhumatoïde, spondylarthrite ankylosante, arthrite psoriasique et arthrose ou maladie articulaire dégénérative, syndrome de Reiter, syndrome de Sjögren, syndrome de Behçet, polychondrite récidivante, lupus systémique érythémateux, lupus discoïde érythémateux, sclérose systémique, fasciite à éosinophiles, polymyosite, dermatomyosite, polymyalgie rhumatismale, vascularite, arthrite temporaire, poly-artérite noueuse, granulomatose de Wegener, maladies mixtes du tissu conjonctif et polyarthrite rhumatoïde juvénile), une maladie ou un symptôme inflammatoire du tube digestif [maladie de Crohn, colite ulcéreuse, syndrome de l'intestin irritable (côlon spastique), fibrose du foie, inflammation de la muqueuse orale (stomatite et stomatite aphteuse récurrente)], une maladie ou un symptôme inflammatoire du système nerveux central (sclérose en plaques, maladie d'Alzheimer et lésion d'ischémie-reperfusion associée à un accident vasculaire cérébral ischémique), une maladie ou un symptôme inflammatoire du poumon (asthme, syndrome de détresse respiratoire de l'adulte, bronchopneumopathies chroniques obstructives), maladie associée au métabolisme des glucides (diabète et complications dérivées du diabète (neuropathie diabétique, néphropathie diabétique)) y compris une maladie des microvaisseaux et des gros vaisseaux (artériosclérose, rétinopathie, néphropathie, syndrome néphrotique et neuropathie (neuropathie multiple, mononeuropathie et neuropathie autonome), ulcère du pied, problème articulaire et augmentation du risque d'infection), une maladie associée à une anomalie dans la différenciation ou la fonction des adipocytes ou la fonction des cellules des muscles lisses (artériosclérose et obésité), une maladie vasculaire [athérosclérose athéromateuse, maladie athéroscléreuse non athéromateuse, maladies cardiaques ischémiques y compris infarctus du myocarde et obstruction des artères périphériques, maladie de Raynaud et phénomène de Raynaud, thromboangéite oblitérante (maladie de Buerger)], une arthrite chronique, une maladie inflammatoire de l'intestin, ou des complications médiées par la SSAO [diabète (diabète insulinodépendant (DID) et diabète non insulinodépendant (DNID)] et des complications vasculaires (crise cardiaque, angine de poitrine, apoplexie, amputation, cécité et insuffisance rénale)], une maladie ophtalmique associée à une hypoxie ou à une ischémie [rétinopathie du prématuré, rétinopathie diabétique proliférante, vasculopathie choroïdienne polypoïdale, prolifération angiomateuse rétinienne, occlusion de l'artère rétinienne, occlusion de la veine rétinienne, maladie de Coats, vitréorétinopathie exsudative rétinienne, maladie sans pouls (maladie de Takayasu), maladie de Eales, syndrome des anticorps antiphospholipides, rétinopathie leucémique, syndrome de l'hyperviscosité sanguine, macroglobulinémie, rétinopathie associée aux interférons, rétinopathie hypertensive, rétinopathie due à des radiations, déficience des cellules souches épithéliales de la cornée] ou la cataracte.

REFERENCES CITED IN THE DESCRIPTION

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