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(54) **TRICYCLIC SPIRO COMPOUND**

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(56) References cited:

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- DATABASE REGISTRY [Online] 18 March 2014
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Description

TECHNICAL FIELD

[0001] The present invention relates to an EP₄ receptor antagonist tricyclic spiro compound, a salt thereof, or a solvate thereof, and to a medicament containing such a compound as an active ingredient. Specifically, the invention relates to a compound selected from 4-[4-cyano-2-({[(2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid, a salt, or a solvate thereof (hereinafter, these will be referred to as "present compounds"), and to a medicament containing such a compound as an active ingredient.

BACKGROUND ART

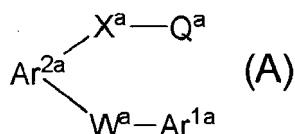
[0002] The prostaglandin E₂ (PGE₂), a known metabolite of the arachidonic acid cascade, is known to have a range of effects including cytoprotection, uterine contraction, lowering of the threshold of pain, promotion of peristalsis in the digestive tract, wakefulness, inhibition of stomach acid secretion, hypotensive effect, and diuretic effect.

[0003] Recent studies have found that there are subtypes of PGE₂ receptors with different roles. To date, four broad subtypes are known, and these are called EP₁, EP₂, EP₃, and EP₄ (Journal of Lipid Mediators and Cell Signalling, Vol. 12, p. 379-391, 1995).

[0004] In these subtypes, the EP₄ receptor is thought to be involved in inhibition of MCP-1 production from macrophages, inhibition of TNF- α , IL-2, and IFN- γ production from lymphocytes. This subtype is also believed to have involvement in anti-inflammation by enhanced IL-10 production, vasodilatation, angiogenesis, inhibition of elastic fiber formation, and regulation of MMP-9 expression. Other possible involvement of the EP₄ receptor includes immune control in cancer via myeloid derived suppressor cells, regulatory T cells, and natural killer cells.

[0005] It is therefore thought that compounds that strongly bind to the EP₄ receptor, and show antagonistic activity are useful for the prevention and/or treatment of diseases caused by EP₄ receptor activation, including, for example, a bone disease, a cancer, a systemic granulomatous disease, an immune disease, allergy, atopy, asthma, alveolar pyorrhea, gingivitis, periodontitis, Alzheimer's, Kawasaki disease, burn, multiple organ failure, chronic headache, pain, vasculitis, venous incompetence, varicose veins, aneurysm, aortic aneurysm, anal fistula, diabetes insipidus, stress, endometriosis, uterine adenomyosis, patent ductus arteriosus in neonates, and cholelithiasis (Pharmacological Reviews, Vol. 65, p. 1010-1052, July, 2013; 105th Annual Meeting of American Association for Cancer Research (AACR), Abstract: LB-265, Title of Presentation: ONO-AE3-208 Inhibits Myeloid Derived Suppressor Cells and Glioma Growth, Date of Presentation: April 8, 2014; FEBS Letters, Vol. 364, p. 339-341, 1995; Cancer Science, Vol. 105, p. 1142-1151, 2014; Cancer Research, Vol. 70, p. 1606-1615, 2010; and Cancer Research, Vol. 62, p. 28-32, 2002).

[0006] WO2000/020371 describes a compound of the following general formula (A) used for the treatment of diseases involving prostaglandin E receptors, for example, such as pain, inflammation, and cancer.



In the general formula (A),

Ar^{1a} is an aryl or a heteroaryl group optionally substituted with R^{1a} or R^{3a}, wherein R^{1a} is CN, NO₂, CON(R^{5a})₂, or the like;

W^a represents a three- to six-membered linking group containing 0 to 2 heteroatoms selected from O, N, and S, wherein the linking group optionally contains CO, S(O)_{na}, C=C, or an acetylene group;

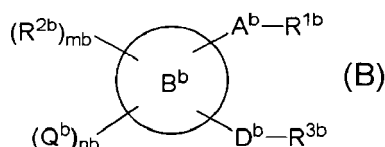
Ar^{2a} is an aryl or a heteroaryl group optionally substituted with R^{3a}, wherein R^{3a} is halogen, CN, or the like;

X^a is a linker attached to Ar^{2a} at the position ortho to the bonding site for W^a; and

Q^a is COOH or the like

(These are only a part of the definitions of the groups.)

[0007] EP 1312601 is directed EP₄ receptor antagonists. WO2003/016254 describes a compound of the following general formula (B) that binds to the PGE₂ receptor, particularly EP₃ and/or EP₄, and has antagonistic activity, useful for the prevention and/or treatment of diseases such as pain, and cancer.



In the general formula (B),

R^{1b} represents -COOH or the like;

A^b represents (i) a single bond, (ii) C1-6 alkylene, (iii) C2-6 alkenylene, (iv) C2-6 alkynylene, or the like;

the ring B^b represents a C3-12 monocyclic or bicyclic carbon ring, or a three- to twelve-membered monocyclic or bicyclic heterocyclic ring;

R^{2b} represents nitro, cyano, or the like;

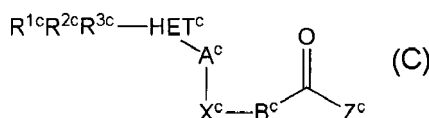
Q^b represents C2-6 alkenyl, C2-6 alkynyl, C1-6 alkyl substituted with 1 to 3 halogen atoms, cyano, nitro, or the like;

D^b is a one- or two-membered linking chain of atoms selected from a carbon atom, a nitrogen atom, an oxygen atom, and a sulfur atom, wherein the linking chain may contain a double bond or a triple bond, and may be substituted with one to four R^{40b}, wherein R^{40b} represents an oxo, halogen, or the like; and

R^{3b} represents (1) C1-6 alkyl, or (2) a C3-15 monocyclic, bicyclic, or tricyclic carbon ring that is substituted with one to five R^{42b}, or that is unsubstituted, or a three- to fifteen-membered monocyclic, bicyclic, or tricyclic heterocyclic ring, wherein R^{42b} represents C1-6 alkyl, C1-6 alkoxy, halogen, cyano, -NR^{46b}COR^{47b}, or Cyc10^b.

(These are only a part of the definitions of the groups.)

[0008] WO1999/047497 describes a compound of the following general formula (C) used for the treatment of diseases involving prostaglandin E receptors, for example, such as pain, inflammation, and cancer.



In the general formula (C),

HET^c represents a five- to twelve-membered monocyclic or bicyclic aromatic ring system having 0 to 3 heteroatoms selected from O, S(O)_{nc}, and N(O)_{mc}, wherein mc is 0 or 1, and nc is 0, 1, or 2;

A^c is one- or two-atom moiety and is selected from the group including -W^c- and -C(O)-, wherein W^c is O, S(O)_{nc}, or NR^{17c};

X^c represents a five- to ten-membered monocyclic or bicyclic aryl or heteroaryl group having 1 to 3 heteroatoms selected from O, S(O)_{nc}, and N(O)_{mc};

Y^c represents O, S(O)_{nc}, NR^{17c}, a bond, or the like;

B^c is - (C(R^{18c})₂)_{pc}-Y^c- (C(R^{18c})₂)_{qc}-, wherein pc and qc are independently 0 to 3;

Z^c is OH, or the like; and

R^{1c}, R^{2c}, and R^{3c} independently represent halogen, -CO₂R^{9c}, -CON(R^{6c})₂, or the like.

(These are only a part of the definitions of the groups.)

[0009] None of these related art documents describe or suggest the present compound, specifically, the tricyclic spiro compound.

CITED REFERENCES

PATENT DOCUMENTS

[0010]

PATENT DOCUMENT 1: WO2000/020371

PATENT DOCUMENT 2: WO2003/016254

PATENT DOCUMENT 3: WO1999/047497

NON-PATENT DOCUMENTS

[0011]

- 5 NON-PATENT DOCUMENT 1: Journal of Lipid Mediators and Cell Signalling, Vol. 12, p. 379-391, 1995
 NON-PATENT DOCUMENT 2: Pharmacological Reviews, Vol. 65, p. 1010-1052, July, 2013
 NON-PATENT DOCUMENT 3: 105th Annual Meeting of American Association for Cancer Research (AACR), Abstract: LB-265, Title of Presentation: ONO-AE3-208 Inhibits Myeloid Derived Suppressor Cells and Glioma Growth, Date of Presentation: April 8, 2014
 10 NON-PATENT DOCUMENT 4: FEBS Letters, Vol. 364, p. 339-341, 1995
 NON-PATENT DOCUMENT 5: Cancer Science, Vol. 105, p. 1142-1151, 2014
 NON-PATENT DOCUMENT 6: Cancer Research, Vol. 70, p. 1606-1615, 2010
 NON-PATENT DOCUMENT 7: Cancer Research, Vol. 62, p. 28-32, 2002

15 DISCLOSURE OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

- 20 **[0012]** The present invention is intended to create compounds that have a strong antagonistic activity against the EP₄ receptor, and show desirable pharmacokinetics, and to find a compound that is useful as a preventive and/or a therapeutic drug for diseases caused by EP₄ receptor activation.

MEANS FOR SOLVING THE PROBLEMS

- 25 **[0013]** In order to achieve the foregoing object, the present inventors conducted intensive studies to find a compound that has a strong antagonistic activity against the EP₄ receptor, and shows desirable pharmacokinetics, and found that compounds of appended claim 1 are strong antagonists of the EP₄ receptor. The present invention was completed on the basis of this finding; The present invention is directed to a compound selected from 4-[4-cyano-2-(((2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl)carbonyl)amino)phenyl]butanoic acid, a salt thereof, and a solvate thereof.
 30 **[0014]** Also provided is a pharmaceutical composition comprising the compound of the present invention as an active ingredient.
[0015] The present invention is further directed to a medicament comprising the compound of with the present invention and at least one selected from an alkylating agent, an antimetabolite, an anti-cancer antibiotic, a plant-based preparation, a hormonal agent, a platinum compound, a topoisomerase inhibitor, a kinase inhibitor, an anti-CD20 antibody, an anti-HER2 antibody, an anti-EGFR antibody, an anti-VEGF antibody, a proteasome inhibitor, an HDAC inhibitor, and an immunomodulator.
 35 **[0016]** The invention also provides the compound of appended claim 1 for use in the prevention and/or treatment of a disease caused by EP₄ receptor activation.
 40 Preferred embodiments of the present invention are set forth in the dependent claims.

EFFECT OF THE INVENTION

- 45 **[0017]** The present compound has a strong antagonistic activity against the EP₄ receptor, and shows desirable pharmacokinetics. The present compound has use as a preventive and/or a therapeutic drug against diseases caused by EP₄ receptor activation.

BRIEF DESCRIPTION OF THE DRAWING

- 50 **[0018]** FIG. 1 is a diagram representing the anti-tumor effect of the present compound in an allograft model of mouse colorectal cancer cell line CT26.

EMBODIMENTS FOR CARRYING OUT THE INVENTION

- 55 **[0019]** The present invention is described below in detail.

Salts

[0020] The compound of the present invention is converted into a salt using a known method.

[0021] The salt is preferably a pharmaceutically acceptable salt.

5 **[0022]** Preferably, the salt is water soluble.

[0023] Examples of the pharmaceutically acceptable salt include acid addition salts, alkali metal salts, alkali-earth metal salts, ammonium salts, and amine salts.

[0024] The acid addition salts may be inorganic acid salts, for example, such as hydrochloride, hydrobromate, hydroiodide, sulfates, phosphates, and nitrates, or organic acid salts, for example, such as acetates, lactates, tartrates, benzoates, citrates, methanesulfonate, ethanesulfonate, trifluoroacetate, benzenesulfonate, toluenesulfonate, isethionates, glucuronates, and gluconates.

[0025] Examples of the alkali metal salts include potassium, and sodium.

[0026] Examples of the alkali-earth metal salts include calcium, and magnesium.

[0027] Examples of the ammonium salts include tetramethylammonium.

15 **[0028]** Examples of the amine salts include triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)aminomethane, lysine, arginine, and N-methyl-D-glucamine.

[0029] The compound 4-[4-cyano-2-({ [(2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl)amino]phenyl]butanoic acid, and a salt thereof may be transformed into a solvate.

20 **[0030]** Preferably, the solvate is non-toxic, and water soluble. Examples of suitable solvates include solvates using water, and solvates using alcoholic solvents (for example, ethanol).

[0031] The atoms constituting the compounds of the present invention may be replaced with their isotopes (for example, ²H, ³H, ¹³C, ¹⁴C, ¹⁵N, ¹⁶N, ¹⁷O, ¹⁸O, ¹⁸F, ³⁵S, ³⁶Cl, ⁷⁷Br, and ¹²⁵I).

25 Method of Production of Present Compounds

[0032] The present compounds may be produced by known methods, for example, by the methods described below, methods equivalent thereto, or the methods described in the Examples below. In the methods of production below, the feed compound may be in the form of a salt. The salt may be any of the pharmaceutically acceptable salts exemplified for the present compounds.

30 **[0033]** The present compounds may be produced by combining the methods described in the Examples described in this specification, or by combining known methods, for example, such as described in Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition (Richard C. Larock, John Wiley & Sons Inc., 1999).

35 Toxicity

[0034] The present compound has low toxicity, and is safe to use as a drug.

40 Drug Applications

[0035] The present invention is intended to create compounds having a strong antagonistic activity against the EP₄ receptor, and that show desirable pharmacokinetics, and to find a compound that is useful as a preventive and/or a therapeutic drug against diseases caused by EP₄ receptor activation.

45 **[0036]** The present compound shows antagonistic activity against the EP₄ receptor, and is useful as a preventive and/or a therapeutic agent against diseases caused by EP₄ receptor activation, for example, such as a bone disease, a cancer, a systemic granulomatous disease, an immune disease, an allergic disease, asthma, alveolar pyorrhea, gingivitis, periodontitis, Alzheimer's, Kawasaki disease, burn, multiple organ failure, chronic headache, pain, vasculitis, venous incompetence, varicose veins, aneurysm, aortic aneurysm, anal fistula, diabetes insipidus, stress, endometriosis, uterine adenomyosis, patent ductus arteriosus in neonates, and cholelithiasis.

50 **[0037]** Specific examples of the bone disease include osteoporosis, rheumatoid arthritis, osteoarthritis, and skeletal dysplasias. Examples of the cancer include breast cancer, ovarian cancer, colorectal cancer (for example, colon cancer), lung cancer (for example, non-small cell cancer), prostate cancer, head and neck cancer (for example, oral squamous cell carcinoma, head and neck squamous cell carcinoma, pharyngeal cancer, laryngeal cancer, tongue cancer, thyroid cancer, acoustic neuroma), lymphoma (for example, B cell lymphoma, T cell lymphoma), uveal melanoma, thymoma, mesothelioma, esophageal cancer, stomach cancer, duodenal cancer, hepatocellular carcinoma, cholangiocarcinoma, gallbladder cancer, pancreatic cancer, renal cell carcinoma, renal pelvis and ureter cancer, bladder cancer, penile cancer, testicular cancer, uterus cancer, vaginal cancer, vulvar cancer, skin cancer (for example, malignant melanoma), malignant bone tumor, soft tissue sarcoma, chondrosarcoma, leukemia (for example, acute myelogenous leukemia, acute lym-

phoblastic leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia), myelodysplastic syndrome, and multiple myeloma. Examples of the immune disease include amyotrophic lateral sclerosis (ALS), multiple sclerosis, Sjogren's syndrome, systemic lupus erythematosus, and AIDS. Examples of the allergic disease include allergic conjunctivitis, allergic rhinitis, contact dermatitis, and psoriasis. Examples of the chronic headache include migraine, tension headache, a combination of these, and cluster headache.

[0038] The present compound may be administered as a concomitant drug with other medicinal agent to:

- 1) complement and/or enhance the preventive and/or therapeutic effect of the compound,
- 2) improve the kinetics and absorption of the compound, and reduce the dose of the compound, and/or
- 3) reduce the side effects of the compound.

[0039] The concomitant drug using the present compound with other medicinal agent may be administered in the form of a compounding agent containing the both components in the same preparation, or in the form of separate preparations. When administered as separate preparations, the preparations may be administered at the same or different times. When administered at different times, the present compound may be administered before other medicinal agent, or other medicinal agent may be administered before the present compound. These may be administered using the same or different method.

[0040] The disease for which the concomitant drug shows a preventive and/or therapeutic effect is not particularly limited, provided that the disease is one in which the preventive and/or therapeutic effect of the present compound is complemented and/or enhanced.

[0041] Examples of medicinal agents that complement and/or enhance the preventive and/or therapeutic effect of the present compound in aortic aneurysm include HMG-CoA reductase inhibitors, antihypertensives, and tetracycline antibiotics.

[0042] Examples of the HMG-CoA reductase inhibitors include pravastatin (sodium), simvastatin, fluvastatin (sodium), cerivastatin (sodium), itavastatin, atorvastatin (calcium hydrate), lovastatin, and pitavastatin (calcium).

[0043] Examples of the antihypertensives include calcium antagonists, angiotensin II antagonists, angiotensin converting enzyme inhibitors, phosphodiesterase 4 inhibitors, diuretics, prostaglandins, aldosterone antagonists, and sympathetic blocking agents.

[0044] Examples of the calcium antagonists include nifedipine, benidipine hydrochloride, diltiazem hydrochloride, verapamil hydrochloride, nisoldipine, nitrendipine, bepridil hydrochloride, amlodipine besilate, lomerizine hydrochloride, and efondipine hydrochloride.

[0045] Examples of the angiotensin II antagonists include losartan (potassium), candesartan (cilexetil), valsartan, irbesartan, olmesartan (medoxomil), and telmisartan.

[0046] Examples of the angiotensin converting enzyme inhibitors include alacepril, imidapril hydrochloride, quinapril hydrochloride, temocapril hydrochloride, delapril hydrochloride, benazepril hydrochloride, captopril, trandolapril, perindopril erbumine, enalapril maleate, and lisinopril.

[0047] Examples of the phosphodiesterase 4 inhibitors include cilomilast, roflumilast, arofyline, atizoram, cipamfylline, and rolipram.

[0048] Examples of the diuretics include acetazolamide, aminophylline, isosorbide, dichlorphenamide, spironolactone, trichlormethiazide, furosemide, mannitol, methazolamide, and mefruside.

[0049] Examples of the aldosterone antagonists include drospirenone, metyrapone, potassium canrenoate, canrenone, and eplerenone.

[0050] Examples of the tetracycline antibiotics include doxycycline.

[0051] Examples of the medicinal agents that complement and/or enhance the preventive and/or therapeutic effect of the present compound in cancer include alkylating agents, antimetabolites, anti-cancer antibiotics, plant-based preparations, hormonal agents, platinum compounds, topoisomerase inhibitors, kinase inhibitors, anti-CD20 antibodies, anti-HER2 antibodies, anti-EGFR antibodies, anti-VEGF antibodies, proteasome inhibitors, HDAC inhibitors, and immunomodulators.

[0052] Examples of the alkylating agents include cyclophosphamide, ifosfamide, dacarbazine, temozolomide, nimustine hydrochloride, ranimustine, bendamustine, thiotepea, and carboquone.

[0053] Examples of the antimetabolites include methotrexate, pemetrexed, fluorouracil, tegafur, tegafur uracil, tegafur gimestat otastat potassium, doxifluridine, capecitabine, cytarabine, gemcitabine hydrochloride, fludarabine, nelarabine, carmofur, and procarbazine hydrochloride.

[0054] Examples of the anti-cancer antibiotics include mitomycin C, doxorubicin hydrochloride, aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin, chromomycin A3, bleomycin, peplomycin sulfate, and therarubicin.

[0055] Examples of the plant-based preparations include irinotecan hydrochloride, etoposide, vincristine sulfate, vinblastine sulfate, vindesine sulfate, vinorelbine tartrate, docetaxelhydrate, eribulin mesylate, and paclitaxel.

[0056] Examples of the hormonal agents include estramustine sodium phosphate, flutamide, bicalutamide, goserelin

acetate, leuprorelin acetate, tamoxifen citrate, toremifene citrate, anastrozole, letrozole, exemestane, mepitiostane, medroxyprogesterone acetate, epitioestanol, fosfestrol, fadrozole hydrochloride hydrate, abiraterone, fulvestrant, and aminoglutethimide.

[0057] Examples of the platinum compounds include carboplatin, cisplatin, nedaplatin, and oxaliplatin.

[0058] Examples of the topoisomerase inhibitors include topotecan, and sobuzoxane.

[0059] Examples of the kinase inhibitors include EGFR inhibitors such as erlotinib, gefitinib, and afatinib; HER2 inhibitors such as lapatinib; BCR-ABL inhibitors such as imatinib; ALK inhibitors such as crizotinib; and multi-kinase inhibitors such as regorafenib, and dasatinib.

[0060] Examples of the anti-CD20 antibodies include rituximab, ibritumomab, ibritumomab tiuxetan, and ocrelizumab.

[0061] Examples of the anti-HER2 antibodies include trastuzumab, trastuzumab emtansine, and pertuzumab.

[0062] Examples of the anti-EGFR antibodies include cetuximab, and panitumumab.

[0063] Examples of the anti-VEGF antibodies include bevacizumab.

[0064] Examples of the proteasome inhibitors include bortezomib.

[0065] Examples of the HDAC inhibitors include vorinostat.

[0066] Examples of the immunomodulators include thalidomide, lenalidomide, and pomalidomide.

[0067] Examples of the medicinal agents that complement and/or enhance the preventive and/or therapeutic effect of the present compound in pain include N-type calcium channel inhibitors, nitrogen oxide synthetase (NOS) inhibitors, and cannabinoid-2 receptor stimulating reagents.

[0068] Examples of the N-type calcium channel inhibitors include cilnidipine.

[0069] Examples of the nitrogen oxide synthetase (NOS) inhibitors include D-arginine, and N^G-monomethyl-L-arginine.

[0070] The mass ratio of the present compound and other medicinal agent is not particularly limited.

[0071] The medicinal agents may be administered in any combination of two or more.

[0072] To use the present invention compounds as a single drug or a companion drug with other drugs for the prevention and/or treatment of said diseases, preparations are usually formed in active substances and various additives or pharmaceutically acceptable excipients, and are administered as oral or parenteral preparation systemically or locally. The pharmaceutically acceptable excipients mean materials except active substances which are generally used for preparations. The pharmaceutically acceptable excipients are preferably excipients which are harmless, and do not show any pharmacological effect and inhibit treatment effect of the active substances at the dosage of the drug products. In addition, the pharmaceutically acceptable excipients can be used to enhance effectiveness of the active substances, make production of the drugs easy, stabilize quality and improve usability. Specifically, the material described in "Iyakuhintenkabutujiten" (yakujinippousha, 2000), (edited by nihonniyakuhintennkazai kyokai)", may be selected according to intentions.

[0073] Dosage forms for administration includes, for example, oral preparation (e.g.: tablets, capsules, granules, powders, oral solutions, syrups, or oral jelly agents), oro-mucosal preparation (e.g.: tablets for oro-mucosal application, sprays for oro-mucosal application, semi-solid preparations for oro-mucosal application, or gargles), preparations for injection (e.g.: injections), preparations for dialysis (e.g.: dialysis agents), preparation for inhalation (e.g.: inhalations), preparation for ophthalmic application (e.g.: ophthalmic liquids and solutions, and ophthalmic ointments), preparation for otic application (e.g.: ear preparation), preparations for nasal application (nasal preparations), preparation for recta (e.g.: suppositories, semi-solid preparations for rectal application, or enemas for rectal application), preparations for vaginal application (e.g.: tablets for vaginal use, or suppositories for vaginal use) and preparation for cutaneous application (e.g.: solid preparations for cutaneous application, liquids and solutions for cutaneous application, sprays, ointment, creams, gels, or patches).

[Oral preparation]

[0074] Oral preparation include, for example, tablets, capsules, granules, powders, liquids and solution for oral administration, syrups, and Jellies for oral administration. As oral preparation, there are Immediate-release dosage forms showing a release pattern of active substances that is not intentionally modified and modified-release dosage forms are preparations showing modified pattern of active substances that is suitably modified for the desired purpose by means of a specific formulation design and/or manufacturing methods. Modified-release dosage forms include enteric-coated and extended-release preparations. Enteric-coated (delayed-release) preparations release the bulk of the active substances not in stomach but mainly in small intestine, in order to prevent degradation or decomposition of the active substances in stomach or to decrease the irritation of the active substances on stomach. Enteric-coated preparations are generally coated with an acid-insoluble enteric film. Extended-release preparations are designed to control the release rate and release period of active substances and to restrict the release to appropriate sites in the gastrointestinal tracts in order to decrease the dosing frequency and/or to reduce adverse or side effects. Extended-release preparations are generally prepared by using suitable agents that prolong the release of the active substances. Oral dosage forms such as capsules, granules and tablets can be coated with appropriate coating agents, such as sugars, sugar alcohols,

or polymers, for the purpose of enabling the ingestion easy or of preventing degradation of the active substances.

(1) Tablets

5 **[0075]** Tablets are solid preparation having a desired shape and size, intended for oral administration, and include orally disintegrating tablets, chewable tablets, effervescent tablets, dispersible tablets, soluble tablets besides generally called tablets such as plain tablets, film-coated tablets, sugar-coated tablets, multi-layered tablets and pressure-coated tablets. Plain tables are usually prepared according to the following methods (a), (b) and (c):

10 (a) Mix homogeneously active substances and excipients such as diluents, binders and disintegrators, granulate with water or a binder solution by suitable methods, mix with a lubricant, and then compress into a desired shape and size;

(b) Mix homogeneously active substances and excipients such as diluents, binders, and disintegrators, and then directly compress, or compress after adding active substances and lubricant to granules previously prepared from excipients and then mixing homogeneously;

15 (c) Mix homogeneously active substances and excipients such as diluents and binders, moisten with a solvent, form into a certain shape and size, and then dry by a suitable methods; Film-coated tablets can be prepared, usually, by coating plain tablets using suitable coating agents such as polymers. Sugar-coated tablets can be prepared, usually, by coating plain tablets using suitable coating agents including sugars and sugar alcohols. Multiple-layer tablets can be prepared by compressing granules of different compositions to form layered tablets by a suitable method. Pressure-coated tablets can be prepared by compressing granules to cover inner core tablets with different compositions. In addition, tablets can be prepared as enteric coated tablets or timed- release tablet by suitable well-known methods. Orally disintegrating tablets, chewable tablets, effervescent tablets, dispersible tablets, soluble tablets are tablets which are added distinct role by selecting suitable excipients, and can be prepared according to said methods. Orally disintegrating tablets are tablets which are quickly dissolved or disintegrated in the oral cavity; Chewable tablets are tablets which are administered by chewing; Effervescent tablets are tablets which are quickly dissolved or dispersed with bubbles in water; Dispersible tablets are tablets which are administered after having been dispersed in water; Soluble tablets are tablets which are administered after having been dissolved in water. Effervescent tablets can be prepared using suitable acidic substances and carbonates or hydrogen carbonates as excipients.

(2) Capsules

35 **[0076]** Capsules are preparations enclosed in capsules or wrapped with capsule bases, intended for oral administration. Capsules are classified into hard capsules and soft capsules. Hard capsules can be prepared by a method where a homogeneous mixture of active substances with diluents and other suitable excipients, or granules or formed masses prepared by a suitable methods, are filled into capsule shells as they are or after slight compression. Soft capsules can be prepared by a method where active substances and suitable excipients are mixed, enclosed by a suitable capsule base such as gelation plasticized by addition of glycerin, or D-sorbitol, and molded in a suitable shape and size. Capsules can be prepared as enteric-coated or extended-release capsules by a suitable well-known method. Coloring agents and preservatives, may be added to the capsule bases.

(3) Granules

45 **[0077]** Granules are preparations prepared by granulation, and include effervescent granules besides generally called granules. Granules can be prepared by the following methods (a), (b), and (c) ;

(a) To powdery active substances add diluents, binders, disintegrators, or other suitable excipients, mix to homogenize, and granulate by a suitable method;

50 (b) To previously granulated active substances add excipients such as diluents, and mix to homogenize;

(c) To previously granulated active substances add excipients such as diluents, and granulate by a suitable method; Granules can be coated if necessary, and can be prepared as enteric-coated or extended-release granules. Effervescent granules can be prepared using suitable acidic substances and carbonates or hydrogen carbonates. Effervescent granules are granules which are quickly dissolved or dispersed with bubbles in water. Granules can be prepared as fine grain agents by adjusting particle size.

(4) Powders

[0078] Powders are preparations in powder form, and are usually prepared by homogeneously mixing active substances with diluents or other suitable excipients.

(5) Liquids and solution for oral administration

[0079] Liquids and solution for oral administration are preparations in liquid form or flowable and viscous gelatinous state, and elixirs, suspensions, emulsions and lemonades are included in this category besides generally called Liquids and solution for oral administration. Liquids and solution for oral administration are usually prepared by dissolving, emulsifying or suspending active substances in purified water together with excipients, and by filtering if necessary. Elixirs are clear, sweetened and aromatic liquid preparations, containing ethanol, and are usually prepared by dissolving solid active substances or their extractives in ethanol and purified water, adding aromatic agents and sucrose, other sugars or sweetening agents, and clarifying by filtration or other procedure. Suspensions are liquid preparations of active substances suspended finely and homogeneously in a vehicle, and are usually prepared by adding suspending agent or other suitable excipients and purified water or oil to solid active substances, and suspending homogeneously as the whole by a suitable method. Emulsions are liquid preparations of active substances emulsified finely and homogeneously in a liquid vehicle, and are usually prepared by adding emulsifying agents and purified water to liquid active substances, and emulsifying finely and homogeneously by a suitable method. In addition, Lemonades are sweet and sour, clear liquid preparations, intended for oral administration.

(6) Syrups

[0080] Syrups are viscous liquid or solid preparations containing sugars or sweetening agents, and include preparation for syrups. Syrups are usually prepared by dissolving, mixing, suspending or emulsifying active substances in a solution of sucrose, other sugars or sweetening agents, or in simple syrup. Where necessary, the mixture is boiled, and filtered while hot. Preparations for syrups are preparations in form of granules or powders, which becomes syrups by adding water. They may be termed "dry syrups". Preparations for syrups are usually prepared with sugars or sweetening agents according to said preparation method of granules or powders.

(7) Jellies for oral administration

[0081] Jellies for oral administration are non-flowable gelatinous preparations having a certain shape and size, and usually prepared by mixing active substances with suitable excipients and polymer gel base, gelatinizing and forming into a certain shape and size by a suitable method.

[Preparation for oro-mucosal application]

(1) Tablets for oro-mucosal application

[0082] Tablets for oro-mucosal application are solid preparations having a certain form, and include troches/lozenges, sublingual tablets, buccal tablets, mucoadhesive tablets and medicated chewing gums. Preparations for oro-mucosal application are usually prepared according to said method of tablets. Troches/lozenges are tablets for oro-mucosal application, which are gradually dissolved or disintegrated in the mouth; Sublingual tablets are tablets for oro-mucosal application, from which active substances are quickly dissolved sublingually and absorbed via the oral mucosa; Buccal tablets are tablets for oro-mucosal applications, from which the active substances are dissolved gradually between the cheek and teeth, and absorbed via the oral mucosa; Mucoadhesive tablets are tablets for oro-mucosal application that are applied by adhesion to the oral mucosa; Medicated chewing gums are tablets for oro-mucosal application, releasing active substances by chewing.

(2) Spray for oro-mucosal application

[0083] Spray for oro-mucosal application are preparation that are applied active substances by spraying into the oral cavity in mist, powder, foam or paste forms, and are usually prepared by dissolving or suspending active substances and suitable excipients in a solvent, filter, where necessary, and fill into a container together with liquefied or compressed gas, or dissolving or suspending active substances and suitable excipients in a solvent, and fill into a container, and fit with a pump for spraying.

(3) Semi-solid preparations for oro-mucosal application

[0084] Semi-solid preparations for oro-mucosal application are preparation in cream, gel or ointment forms, intended for application to the oral mucosa. Semi-solid preparations for oro-mucosal application are usually prepared by emulsifying active substances together with excipients using purified water and oil component such as petrolatum, or by homogenizing active substances together with suitable excipients using polymer gel or oil and fats as the base. Creams are semi-solid preparations, which are in the form of oil-in-water or water-in-oil emulsions. Hydrophobic preparations in the form of water-in-oil emulsions may be termed "Oily creams". Creams are usually prepared by mixing homogeneously and emulsifying an oil-phase component and a water-phase component, both warmed, of which either one contains the active substances. There components have the following constituents. Oil-phase component: Vaseline, and fatty alcohols, with or without emulsifying agents or other suitable excipients. Water-phase component: purified water with or without emulsifying agents or other suitable excipients. Gels are gelatinous preparations. There are aqueous gels and oily gels. Aqueous gels are usually prepared by adding polymers, other excipients and purified water to active substances, dissolving or suspending, and gelatinizing by warming and cooling or by adding gelatinizing agents. Oily gels are usually prepared by adding liquid oily bases such as glycols, fatty alcohols and other excipients to active substances and mixing. Ointments are semi-solid preparations, which dissolve or disperse active substances in a base. There are two types, hydrophobic ointments and hydrophilic ointments. Hydrophobic ointments are usually prepared by warming to melt hydrophobic bases such as fatty oils, waxes or paraffin, adding and mixing active substances in the base to be dissolved or dispersed, and kneading the whole to make homogeneous. Hydrophilic ointments are usually prepared by warming to melt hydrophilic bases such as macrogol, adding and mixing active substances in the bases, and kneading the whole to make homogenous.

(4) Preparations for gargle

[0085] Preparations for gargle are liquid preparations intended to apply locally to the oral and throat cavities. Solid type preparations to be dissolved in water before use are also included in this category. Preparations for gargle are usually prepared by dissolving active substances in a solvent together with suitable excipients, and filtering where necessary. Solid preparations are prepared according to said method of tablets or granules.

[Preparation for injection]

(1) Injections

[0086] Injections are sterile preparations to be administered directly into the body through skin, muscle or blood vessel, usually in form of a solution, a suspension or an emulsion of active substances, or of a solid that contains active substances to be dissolved or suspended before use, and include freeze-dried injections, powders, prefilled syringes, cartridges, parenteral infusions, implants/pellets and prolonged-release injections besides generally called injections. Injections are prepared by the following method (a) and (b) :

(a) Dissolve, suspend or emulsify active substances with or without excipients in water for injection or an aqueous or non-aqueous vehicle homogeneously, fill into containers for injection, seal, and sterilize.

(b) Dissolve, suspend or emulsify active substances with or without excipients in water for injection or an aqueous or non-aqueous vehicle, and filtrate aseptically, or prepare aseptically a homogeneous liquid, fill into containers for injection, and seal;

Freeze-dried injections are usually prepared by dissolving active substances with or without excipients such as diluents in water for injection, sterilizing the solution by aseptic filtration, filling the filtrate directly into individual containers for injection and being freeze-dried, or dividing the filtrate in special containers, being freeze-dried and transferred into individual containers for injection. Powder for injections are usually prepared by filtrating aseptically a solution of active substances, obtaining powders by crystallization from the solution or mixing additionally the powders with sterilized excipients, and filling the powders into individual containers for injections. Prefilled syringes for injections are usually prepared by dissolving, suspending or emulsifying active substances with or without excipients in a vehicle, and filling into syringes. Cartridges are used by fixing in an injection device for exclusive use. Cartridges for injection are usually prepared by dissolving, suspending or emulsifying active substances with or without excipients in a vehicle, and filling into cartridges. Parenteral infusions are usually injections of not less than 100 mL, intended for intravenous administration. Implants/Pellets are solid or gel-like form injections, intended for subcutaneous or intramuscular administration by means of an implant device or operative treatment, for the purpose of releasing active substances for a long period of time. Implants/Pellets are usually prepared in a form of pellet, microsphere or gel using biodegradable polymers. Prolonged release injections are injections to be used for intra-

muscular administration, for the purpose of releasing active substances for a long period of time, and usually prepared by dissolving or suspending active substances in a non-aqueous vehicle such as vegetable oil, or by suspending microspheres prepared with biodegradable polymers.

[Preparations for dialysis]

(1) Dialysis agents

[0087] Dialysis agents are preparations in liquid, or in solid which are to be dissolved before use, intended for peritoneal dialysis or hemodialysis, and include peritoneal dialysis agents and hemodialysis agents. Peritoneal dialysis agents are sterile dialysis agents, intended to be used for peritoneal dialysis, and are usually prepared by dissolving active substances with suitable excipients in a vehicle to make a certain volume, or by filling active substances combined with suitable excipients in a container, and sealing it. Sterilize if necessary. In the case of solid preparations to be dissolved before use, it can be prepared according to said preparation method of tablets or granules. Hemodialysis agents are dialysis agents to be used for hemodialysis, and are usually prepared by dissolving active substances with excipients in a vehicle to make a certain volume, or by filling active substances with excipients in a container. In the case of the solid preparations to be dissolved before use, it can be prepared according to said preparation method of tablets or granules.

[Preparation for inhalation]

(1) Inhalations

[0088] Inhalations are preparations intended for administration as aerosols to the bronchial tubes or lung. Inhalations are classified to dry powder inhalers, inhalation liquid preparations and metered-dose inhalers. Dry powder inhalers are preparations which deliver a constant respiratory intake, intended for administration as solid particle aerosols, and are usually prepared by pulverizing active substances into fine particles. Where necessary, lactose or other suitable excipients are added to make homogeneous mixture. Inhalation liquid preparations are liquid inhalations which are administered by an inhalation device such as operating nebulizer. Inhalation liquid preparations are usually prepared by mixing active substances with a vehicle and suitable isotonic agents and/or pH adjusting agents to make a solution or suspension, and by filtering where necessary. Metered-dose inhalers are preparations which deliver a constant dose of active substances from the container together with propellant filled in. Metered-dose inhalers are usually prepared by dissolving active substances with a suitable dispersing agents and stabilizers in a vehicle to make a solution or suspension, and by filling in pressure-resistant containers together with liquid propellant, and setting metering valves.

[Preparation for Ophthalmic application]

(1) Ophthalmic liquids and solutions

[0089] Ophthalmic liquids and solutions are sterile preparations of liquid, or solid to be dissolved or suspended before use, intended for application to the conjunctival sac or other ocular tissues. Ophthalmic liquids and solutions are usually prepared by dissolving, suspending active substances in a vehicle after adding excipients to make a constant volume, or mixing active substances and excipients, and filling into containers.

(2) Ophthalmic ointments

[0090] Ophthalmic ointments are sterile preparations of semi-solid, intended for application to the conjunctival sac and other ocular tissues. Ophthalmic ointments are usually prepared by mixing homogeneously solution of or finely powdered active substances with petrolatum or other bases, and filling into containers.

[Preparation for Otic application]

(1) Ear preparation

[0091] Ear preparations are liquid, semi-solid, or solid preparations which are to be dissolved or suspended before use, intended for application to the external or internal ear. Ear preparations are usually prepared by filling in containers with liquids in which active substances and excipients are dissolved or suspended in a vehicle to make a constant volume, or with powders in which active substances and excipients are mixed.

[Preparations for nasal application]

(1) Nasal preparations

[0092] Nasal preparations are preparations intended for application to the nasal cavities or nasal mucous membrane. Nasal preparations are classified into Nasal dry powder inhalers and Nasal liquid preparations. Nasal dry powder inhalers are fine powdered preparations, intended for application to the nasal cavities. Nasal dry powder inhalers are usually prepared by pulverizing active substances into moderately fine particles, or by mixing homogeneously with excipients where necessary. Nasal liquids and solutions are liquid preparations, or solid preparations to be dissolved or suspended before use, intended for application to the nasal cavities. Nasal liquids and solutions are usually prepared by dissolving or suspending active substances in a vehicle together with excipients, and filtering where necessary. Isotonic agents and/or pH adjusting agents may be used.

[Preparations for rectal application]

(1) Suppositories for rectal application

[0093] Suppositories for rectal application are semi-solid preparations of a desired shape and size, intended for intra-rectal application, which release active substances by melting at body temperature or dissolving or dispersing gradually in the secretions. Suppositories for rectal application are usually prepared by mixing homogeneously active substances and excipients such as dispersing agents and emulsifying agents, dissolving or suspending uniformly in a base which is liquefied by warming, filling a constant volume of the resultant material into containers, and molding it into a shape and size. Lipophilic bases or hydrophilic bases are usually used.

(2) Semi-solid preparations for rectal application

[0094] Semi-solid preparations for rectal application are preparations which are in a form of cream, gel or ointment intended for application to around or inside of the anus. Semi-solid preparations for rectal application are usually prepared by emulsifying active substances with excipients in purified water and oil component such as Vaseline, or by homogeneously mixing active substances and excipients in a base of polymer gel or grease. Creams for rectal application are usually prepared by mixing homogeneously and emulsifying an oil-phase component (such as vaseline, and fatty alcohols) and a water phase component (such as purified water with or without emulsifying agents or other suitable excipients), both warmed, of which either one contains the active substances. Gels for rectal application are gelatinous preparation. There are aqueous gels and oily gels. Aqueous gels are prepared adding polymers, other excipients and purified water to active substances, and dissolving or suspending, and gelatinizing by warming and cooling or by adding gelatinizing agents. Oily gels are prepared by adding liquid oily bases such as glycols, fatty alcohols and other excipients to active substances and mixing. Ointments for rectal application are semi-solid preparations, which dissolve or disperse active substances in a base. There are two types, hydrophobic ointment and hydrophilic ointments. Hydrophobic ointments are usually prepared by warming to melt hydrophobic bases such as fatty oils, waxes or paraffin, adding and mixing active substances in the bases to be dissolved or dispersed, and kneading the whole to make homogeneous. Hydrophilic ointments are usually prepared by warming to melt hydrophilic bases such as macrogol, adding and mixing active substances in the bases, and kneading the whole to make homogeneous.

(3) Enemas for rectal application

[0095] Enemas for rectal application are preparations in liquid form or viscous and gelatinous state, intended for applications via anus. Enemas for rectal application are preparations are usually prepared by dissolving or suspending active substances in purified water or suitable aqueous vehicle to make a given volume, and filling in containers. Dispersing agents, stabilizers and/or pH adjusting agents may be used.

[Preparations for vaginal application]

(1) Tablets for vaginal use

[0096] Tablets for vaginal use are solid applications of a desired shapes and size, intended for application to the vagina, which release active substances by dissolving or dispersing gradually in the secretions. Tablets for vaginal use are usually prepared according to said preparation method of tablets.

(2) Suppositories for vaginal use

[0097] Suppositories for vaginal use are semi-solid preparations of a desired shapes and size, intended for application to the vagina, which release active substances by melting at body temperature or by dissolving or dispersing gradually in the secretions. Suppositories for vaginal use are usually prepared according to said preparation method of suppositories for rectal applications.

[Preparation for cutaneous application]

(1) Solid preparations for cutaneous application

[0098] Solid preparations for cutaneous application are solid preparations intended for application to the skin (including scalp) or nails. Powders for cutaneous application are included in this category. Powders for cutaneous application are powdery solid preparations intended for external application. Powders for cutaneous application are usually prepared by mixing homogeneously active substances and excipients such as diluents and pulverizing the mixture.

(2) Liquids and solutions for cutaneous application

[0099] Liquids and solutions for cutaneous application are liquid preparations intended for application to the skin (including scalp) or nails. Liniments and lotions are included in this category. Liquids and solutions for cutaneous application are usually prepared by mixing active substances and excipients in a vehicle, and filtering if necessary. Liniments are liquid or muddy preparations intended for external application to the skin by rubbing. Lotions are external liquids in which active substances are dissolved, emulsified or finely dispersed in an aqueous vehicle. Lotions are usually prepared by dissolving, suspending or emulsifying active substances in purified water with excipients and making homogeneous as a whole.

(3) Spray for cutaneous application

[0100] Spray for cutaneous application are preparations intended for spraying active substances onto the skin in mists, powders, forms or paste state. Spray for cutaneous application are classified into aerosols for cutaneous application and pump sprays for cutaneous application. Spray for cutaneous applications are usually prepared by dissolving or suspending active substances in a vehicle, filtering where necessary, and filling in containers. Aerosols for cutaneous application are sprays which atomize active substances together with liquefied or compressed gas filled in containers. Aerosols for cutaneous application are usually prepared by dissolving or suspending active substances in a vehicle, filling with liquefied propellants in pressure-resistant containers, and setting a continuous spray valve. If necessary, dispersing agents and stabilizer may be used. Pump sprays for cutaneous application are sprays which atomize active substances in containers by pumping. Pump sprays for cutaneous application are usually prepared by dissolving or suspending active substances with excipients in a vehicle, filling in containers and setting pumps to the containers.

(4) Ointments

[0101] Ointments are semi-solid preparations to be applied to the skin, which dissolve or disperse active substances in a base. There are two types, hydrophobic ointments and hydrophilic ointments. Hydrophobic ointments are usually prepared by warming to melt hydrophobic bases such as fatty oils, waxes or paraffin, adding and mixing active substances in the base to be dissolved or dispersed, and Kneading the whole to make homogeneous. Hydrophilic ointments are usually prepared by warming to melt hydrophilic bases such as macrogol, adding and mixing active substances in the bases, and kneading the whole to make homogenous.

(5) Creams

[0102] Creams are semi-solid preparations to be applied to the skin, which are in the form of oil-in-water or water-in-oil emulsions. Hydrophobic preparations in the form of water-in-oil emulsions may be termed "Oily creams". Creams are usually prepared by mixing homogeneously and emulsifying an oil-phase component and a water-phase component, both warmed, of which either one contains the active substances. There components have the following constituents. Oil-phase component: Vaseline, and fatty alcohols, with or without emulsifying agents or other suitable excipients. Water-phase component: purified water with or without emulsifying agents or other suitable excipients.

(6) Gels

[0103] Gels are gelatinous preparations intended for application to the skin. There are aqueous gels and oily gels. Aqueous gels are usually prepared by adding polymers, other excipients and purified water to active substances, dissolving or suspending, and gelatinizing by warming and cooling or by adding gelatinizing agents. Oily gels are usually prepared by adding liquid oily bases such as glycols, fatty alcohols and other excipients to active substances and mixing.

(7) Patches

[0104] Patches are preparations intended to be attached on the skin. Patches are classified into Tapes/Plasters and Cataplasms/Gel patches. Patches are usually prepared by mixing active substances homogeneously with a base such as a polymer or a mixture of polymers, spreading on a backing layer or liner, and cutting into a given size. Percutaneous absorption type preparations may be prepared by using a release rate-controlling membrane. Where necessary, adhesive agents or penetration enhancers may be used. Tapes/Plasters are patches which are prepared with bases of practically no water contain. Tapes/Plasters are usually prepared by mixing homogeneously active substances with or without excipients and a base of non water-soluble natural or synthetic polymers such as resins, plastics or rubber, and spreading on a cloth or spreading and sealing on a cloth or plastic film, cutting into a given size. The preparations may be also prepared by filling a mixture of active substances and a base with or without other excipients in releasers composed with a release-controlling film, supporter and liner. Cataplasms/Gels are patches using water containing bases. Cataplasms/Gels patches are usually prepared by mixing active substances, purified water, and glycerin or other liquid materials, or by mixing and kneading natural or synthetic polymers, which are soluble in water or absorbent of water, with purified water, adding active substances, mixing the whole homogeneously, spreading on a cloth or film, and cutting into a given size.

[0105] Unless otherwise defined, all technical and scientific terms, and all abbreviations used in this specification have the meaning as normally understood by a skilled person in the art to which the present invention pertains.

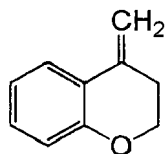
EXAMPLES

[0106] The present invention is described below in greater detail by way of Examples.

[0107] The solvents in parentheses shown in connection with the separation positions in chromatography and with TLC represent the eluting solvents or developing solvents used. The proportions are volume ratios.

[0108] The solvents in parentheses shown in connection with NMR represent the solvents used for measurement.

[0109] As a rule, the compound names used in this specification are based on the computer program ACD/Name® or the Chemdraw Ultra (version 12.0, Cambridge Soft), which generate chemical names according to IUPAC rules. The compound names are also based on the IUPAC nomenclature.

Reference Example 1: 4-Methylenechromane**[0110]**

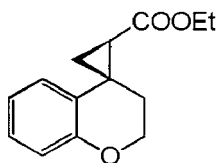
[0111] A solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (hereinafter, "THF") (1.3 mol/L, 931 mL) was dropped into a 1,500-mL THF solution of methyltriphenylphosphonium bromide (435 g) under a stream of nitrogen on ice, and the mixture was stirred at room temperature for 1 h. The mixture was further stirred at room temperature for 1 h after dropping a 180-mL THF solution of 4-chromanone (150 g) at -5°C. After adding a saturated ammonium chloride aqueous solution to the reaction mixture on ice, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was then purified by silica gel column chromatography to obtain the title compound (75.9 g) having the following physical property values.

TLC: R_f 0.62 (hexane:ethyl acetate = 9:1);

¹H-NMR (CDCl₃) : δ 2.59-2.75, 4.18-4.31, 4.89, 5.51, 6.79-6.94, 7.12-7.20, 7.56.

Reference Example 2: Ethyl (2'R,4S)-2,3-dihydrospiro[chromene-4,1'-cyclopropane]-2'-c arboxylate

[0112]

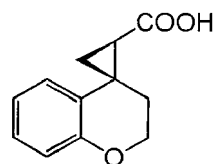


[0113] Under a stream of nitrogen, a dichloro(p-cymene)ruthenium(II) dimer (15.8 g), and (S,S)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)pyridine (15.6 g) were added to a dichloromethane solution (2,500 mL) of the compound (75.9 g) produced in Reference Example 1. A dichloromethane solution (150 mL) of diazoethyl acetate (containing 13% of dichloromethane, 134 g) was then slowly dropped at room temperature, and the mixture was stirred for 1 h. After adding a saturated ammonium chloride aqueous solution to the reaction mixture, the mixture was extracted with dichloromethane, and the organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was then purified by silica gel column chromatography to obtain the title compound (91.2 g) having the following physical property values.

$^1\text{H-NMR}$ (CDCl_3) : δ 1.26, 1.54-1.67, 2.07-2.22, 4.05-4.21, 4.27, 6.68, 6.78-6.89, 7.04-7.12.

Reference Example 3: (2'R,4S)-2,3-Dihydrospiro[chromene-4,1'-cyclopropane]-2'-c arboxylic acid

[0114]



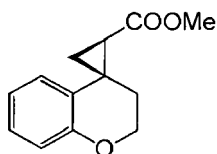
[0115] An aqueous solution (160 mL) of lithium hydroxide monohydrate (29.6 g) was added to a methanol (400 mL) and 1,2-dimethoxyethane (400 mL) solution of the compound (91.2 g) produced in Reference Example 2, and the mixture was stirred overnight at room temperature. A 10% aqueous solution of citric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was then recrystallized with dichloromethane to obtain the title compound (55.2 g) having the following physical property values.

$^1\text{H-NMR}$ (CDCl_3) : δ 1.59-1.67, 1.68-1.76, 2.15, 2.21-2.29, 4.12-4.23, 4.25-4.36, 6.70, 6.80-6.92, 7.06-7.16;

HPLC retention time: 6.9 min (CHIRALPAK IC 4.6 mm $\times$ 250 mm hexane:ethyl acetate:formic acid = 97:3:1).

Reference Example 4: Methyl (2'R,4S)-2,3-dihydrospiro[chromene-4,1'-cyclopropane]-2'-c arboxylate

[0116]



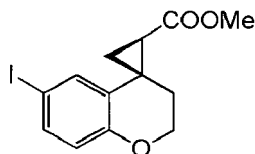
[0117] Under a stream of nitrogen, potassium carbonate (28.5 g) was added to an N,N-dimethylformamide (hereinafter, "DMF") solution (200 mL) of the compound (40.0 g) produced in Reference Example 3. The mixture was stirred overnight at room temperature after dropping iodomethane (31.9 g). The reaction mixture was poured into ice water, and extracted with a hexane-ethyl acetate mixed solution. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (40.1 g) having the following physical property values.

TLC: Rf 0.30 (hexane:ethyl acetate = 9:1);

$^1\text{H-NMR}$ (CDCl_3) : δ 1.57-1.69, 2.09-2.22, 3.71, 4.07-4.17, 4.27, 6.68, 6.78-6.90, 7.04-7.14.

Reference Example 5: Methyl (2'R,4S)-6-iodo-2,3-dihydrospiro[chromene-4,1'-cyclopropan e]-2'-carboxylate

[0118]



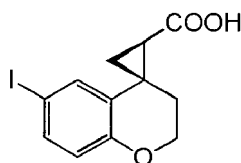
[0119] Under a stream of nitrogen, 1,3-diiodo-5,5-dimethylhydantoin (35.6 g), and three droplets of concentrated sulfuric acid were added to a methanol solution (320 mL) of the compound (40.1g) produced in Reference Example 4, on ice. The mixture was stirred for 1.5 h under the same condition, and for 2.5 h at room temperature. The reaction mixture was diluted with a hexane-ethyl acetate mixed solution, and washed with a saturated sodium bicarbonate aqueous solution. The aqueous layer was extracted with a hexane-ethyl acetate mixed solution. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (63.8 g) having the following physical property values.

TLC: Rf 0.33 (hexane:ethyl acetate = 9:1);

$^1\text{H-NMR}$ (CDCl_3) : δ 1.60, 2.06-2.19, 3.71, 4.09, 4.20-4.31, 6.59, 6.93, 7.36.

Reference Example 6: (2'R,4S)-6-Iodo-2,3-dihydrospiro[chromene-4,1'-cyclopropan e]-2'-carboxylic acid

[0120]



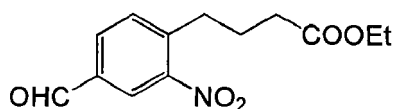
[0121] A sodium hydroxide aqueous solution (2 mol/L, 44 mL) was added to a methanol (60 mL) and 1,2-dimethoxyethane (60 mL) solution of the compound (15.0 g) produced in Reference Example 5, and the mixture was stirred at room temperature for 1.5 h. After adding hydrochloric acid to the reaction mixture, the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain the title compound (14.4 g) having the following physical property values.

TLC: Rf 0.42 (dichloromethane:methanol = 9:1);

$^1\text{H-NMR}$ (CDCl_3) : δ 1.57-1.74, 2.11, 2.16-2.25, 4.10-4.20, 4.23-4.33, 6.59, 6.94, 7.37.

Reference Example 7: Ethyl 4-(4-formyl-2-nitrophenyl)butanoate

[0122]



[0123] Iodine (26.0 g) was added to a 700-mL solution of a zinc powder (99.2 g) in N,N-dimethylacetamide (hereinafter, "DMA") under a stream of nitrogen, and the mixture was stirred for 10 min. After dropping ethyl 4-bromobutyrate (200 g), the mixture was stirred at 80°C for 2 h to prepare a zinc reagent. Under a stream of nitrogen, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (7.14 g), and palladium acetate (1.96 g) were added to a 500-mL THF solution of 3-nitro-4-bromobenzaldehyde (100 g), and the zinc reagent (500 mL) was dropped into the mixture on ice. This was followed by stirring at room temperature for 30 min. A saturated ammonium chloride aqueous solution, and water were added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated

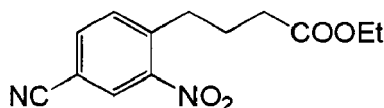
brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was then purified by silica gel column chromatography to obtain the title compound (91.2 g) having the following physical property values.

TLC: Rf 0.61 (hexane:ethyl acetate = 2:1);

$^1\text{H-NMR}$ (CDCl_3) : δ 1.27, 1.97-2.09, 2.42, 3.01, 4.15, 7.57, 8.04, 8.38, 10.03.

Reference Example 8: Ethyl 4-(4-cyano-2-nitrophenyl)butanoate

[0124]



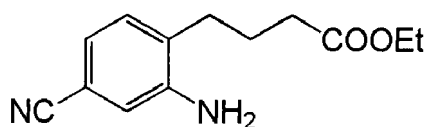
[0125] Hydroxylamine hydrochloride (26.0 g) was added to a 350-mL DMF solution of the compound (92.0 g) produced in Reference Example 7, and the mixture was stirred at 50°C for 1 h. The mixture was stirred at 90°C for 2 h after adding acetyl chloride (30 mL). Then, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, a saturated sodium bicarbonate aqueous solution, and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was then purified by silica gel column chromatography to obtain the title compound (81.0 g) having the following physical property values.

TLC: Rf 0.65 (hexane:ethyl acetate = 2:1);

$^1\text{H-NMR}$ (CDCl_3) : δ 1.27, 1.92-2.10, 2.37-2.45, 2.91-3.06, 4.15, 7.55, 7.81, 8.21.

Reference Example 9: Ethyl 4-(2-amino-4-cyanophenyl)butanoate

[0126]



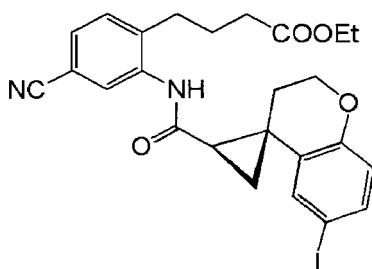
[0127] Palladium carbon (50% wet, 8.0 g) was added to an 80-mL ethanol solution of the compound (17.0 g) produced in Reference Example 8, and the mixture was stirred at room temperature for 9 h in a hydrogen atmosphere. After filtering the reaction mixture with Celite (trade name), the filtrate was concentrated to obtain the title compound (12.0 g) having the following physical property values.

TLC: Rf 0.56 (hexane:ethyl acetate = 2:1);

$^1\text{H-NMR}$ (CDCl_3) : δ 1.28, 1.79-1.95, 2.38-2.45, 2.50-2.60, 4.09-4.30, 6.89, 6.93-6.98, 7.04-7.10.

Reference Example 10 : Ethyl 4-[4-cyano-2-({[(2'R,4S)-6-iodo-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoate

[0128]



[0129] 4-Methylmorpholine (24.0 mL), 4-dimethylaminopyridine (5.33 g), and a propylphosphonic acid anhydride cyclic trimer (hereinafter, "T3P"; 1.7 mol/L, 46.5 mL) were added to a 90-mL DMA solution of the compound (14.4 g) produced

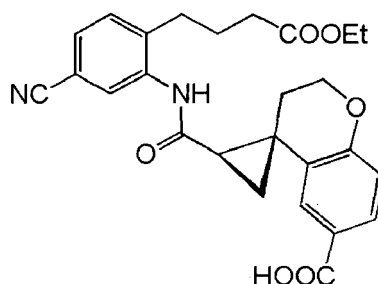
in Reference Example 6, and the compound (10.0 g) produced in Reference Example 9, and the mixture was stirred overnight at room temperature. Ethyl acetate, water, and a hydrochloric acid aqueous solution were added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, a saturated sodium bicarbonate aqueous solution, and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was then washed with a hexane-ethyl acetate mixed solution to obtain the title compound (19.3 g) having the following physical property values.

TLC: Rf 0.42 (hexane:ethyl acetate = 2:1);

$^1\text{H-NMR}$ (CDCl_3): δ 1.20, 1.61, 1.66-1.79, 1.83, 2.18-2.28, 2.39-2.49, 2.60, 3.66, 3.90, 4.00-4.12, 4.26, 6.58, 7.05, 7.15-7.22, 7.26-7.31, 7.33, 8.72, 9.39.

Reference Example 11: (2'R,4S)-2'-[[5-Cyano-2-(4-ethoxy-4-oxobutyl)phenyl]carbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropane]-6-carboxylic acid

[0130]



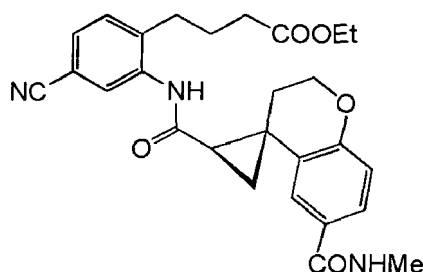
[0131] Sodium acetate (3.35 g), and a [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (555 mg) were added to a 60-mL DMF solution of the compound (7.40 g) produced in Reference Example 10, and the mixture was stirred at 80°C for 6 h in a carbon monoxide atmosphere. A potassium carbonate aqueous solution was added to the reaction mixture, and the mixture was stirred for some time. After adding tert-butyl methyl ether and water, the mixture was filtered with Celite (trade name). A hydrochloric acid aqueous solution was added to the filtrate, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was then purified by silica gel column chromatography (Yamazen Autopurification Device) to obtain the title compound (6.14 g) having the following physical property values.

TLC: Rf 0.48(dichloromethane:ethyl acetate:methanol = 8:4:1) ;

$^1\text{H-NMR}$ (CDCl_3) : δ 1.08, 1.65-1.80, 1.83-1.92, 2.25-2.36, 2.37-2.49, 2.55-2.66, 2.71, 3.55, 3.79, 4.12-4.23, 4.37, 6.88, 7.15 - 7.22, 7.27-7.32, 7.61, 7.83, 8.73, 9.40.

Reference Example 12: Ethyl 4-[4-cyano-2-(((2'R,4S)-6-(methylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropane]-2'-yl)carbonyl)amino]phenyl]butanoate

[0132]

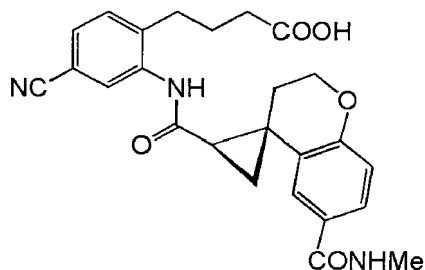


[0133] The title compound (53.0 mg) having the following physical property values was obtained by performing the procedures of Reference Example 10, except that the compound (60.0 mg) produced in Reference Example 11 was used instead of the compound produced in Reference Example 6, and that methylamine hydrochloride (87.5 mg) was used instead of the compound produced in Reference Example 9.

¹H-NMR (CDCl₃) : δ 1.07, 1.64-1.79, 1.81-1.89, 2.20-2.35, 2.40, 2.60, 2.69, 2.98, 3.44-3.59, 3.68-3.83, 4.07-4.19, 4.27-4.38, 6.05, 6.82, 7.15-7.22, 7.27-7.32, 7.35-7.44, 8.72, 9.37.

Comparative Example 1: 4-[4-Cyano-2-(((2'R,4S)-6-(methylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl)carbonyl)amino)phenyl]butanoic acid

[0134]



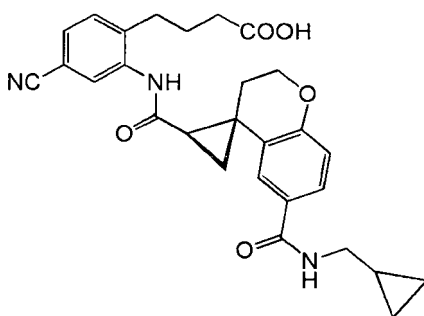
[0135] The title compound (45 mg) having the following physical property values was obtained by performing the procedures of Reference Example 6 using the compound (53 mg) produced in Reference Example 12. Ethanol was used instead of methanol. TLC: R_f 0.45 (dichloromethane:methanol = 9:1);

¹H-NMR (CDCl₃) : δ 1.21-1.30, 1.55, 1.65-1.82, 2.06-2.26, 2.38-2.67, 2.67-2.76, 3.02, 3.57, 4.33, 4.49-4.58, 6.25, 6.81, 7.19, 7.23-7.30, 7.94, 8.87, 9.93.

[0136] The compound of the present invention and the compounds of Comparative Examples 2-1 and 2-2 having the following physical property values were obtained by performing the same procedures from Reference Example 12 to Comparative Example 1, except that the methylamine hydrochloride was replaced with a corresponding amine compound.

Comparative Example 2-1: 4-[4-Cyano-2-(((2'R,4S)-6-[(cyclopropylmethyl)carbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl)carbonyl)amino]phenyl]butanoic acid

[0137]



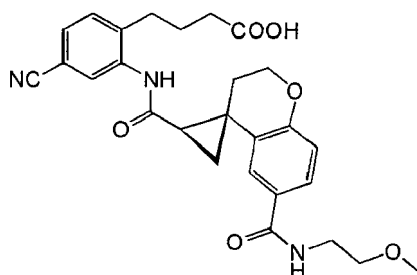
[0138] TLC: R_f 0.45 (dichloromethane:methanol = 9:1);

¹H-NMR (CDCl₃) : δ 0.23-0.31, 0.52-0.63, 0.96-1.14, 1.22-1.30, 1.55, 1.66-1.81, 2.06-2.24, 2.38-2.66, 2.66-2.76, 3.31, 3.57, 4.34, 4.49-4.59, 6.31, 6.83, 7.19, 7.24-7.29, 7.32, 7.95, 8.87, 9.93.

Comparative Example 2-2: 4-[4-Cyano-2-(((2'R,4S)-6-[(2-methoxyethyl)carbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl)carbonyl)amino]phenyl]butanoic acid

[0139]

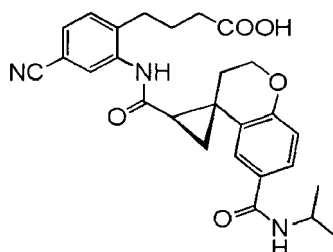
EP 3 243 813 B9



[0140] TLC: Rf 0.51 (dichloromethane:methanol = 9:1);
¹H-NMR (CDCl₃) : δ 1.26, 1.55, 1.67-1.84, 2.06-2.27, 2.39-2.67, 2.67-2.78, 3.39, 3.51-3.78, 4.33, 4.49-4.59, 6.62, 6.82, 7.19, 7.24-7.29, 7.32, 7.92, 8.86, 9.88.

Example 2: 4-[4-Cyano-2-([(2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carboxamyl)phenyl]butanoic acid

[0141]



[0142] TLC: Rf 0.74 (ethyl acetate:methanol = 19:1);
¹H-NMR (CDCl₃) : δ 1.27, 1.34-1.92, 2.01-2.30, 2.38-2.80, 3.50-3.61, 4.18-4.43, 4.54, 6.00, 6.81, 7.15-7.31, 7.94, 8.87, 9.93.

Pharmacological Experiment Examples

Pharmacological Experiment Example 1:

EP₄ Antagonistic Activity Measurement Experiment Using Prostanoid Receptor Subtype Expressing Cells

[0143] CHO cells expressing rat EP₄ receptor subtypes were prepared according to the methods of Nishigaki et al. (FEBS Letters, Vol. 364, p. 339-341, 1995), and used for experiment. Cultured subconfluent cells were detached, and suspended in an assay medium (MEM containing 1 mmol/L IBMX, 1% HSA) in a concentration of 1 × 10⁶ cells/mL. For reaction, PGE₂ was added to the cell suspension (25 μL) in a final concentration of 10 nmol/L, either alone or as a 25-μL PGE₂ solution containing the test compound. After 30 minutes of reaction at room temperature, the amount of cAMP in the cells was quantified according to the method in the descriptions of the cAMP assay kit (CISBIO).

[0144] The antagonistic effect (IC₅₀ value) of the test compound was calculated as a value that represents an inhibition rate against a reaction with PGE₂ alone at 10 nM, a concentration that produces a submaximal cAMP producing effect.

[0145] The present compound was shown to have strong EP₄ receptor antagonistic activity. As examples, Table 1 below shows the IC₅₀ values of some compounds. The EP₄ receptor antagonistic activity was very weak, 2,800 nM, for the compound in Example 8-128 of WO2003/016254.

Table 1

Example	EP ₄ antagonistic activity (IC ₅₀ , nM)
Comp. Ex. 1	2.5
Comp. Ex. 2-2	5.3

(continued)

Example	EP ₄ antagonistic activity (IC ₅₀ , nM)
Example 2	7.8

Pharmacological Experiment Example 2: Pharmacokinetics Test (Hepatic Microsome Stability Test)

(1) Preparation of Subject Substance Solution

[0146] A DMSO solution of the subject substance (the present compound, and a comparative compound) (10 mmol/L; 5 μ L) was diluted with a 50% acetonitrile aqueous solution (195 μ L) to prepare a 250 μ mol/L subject substance solution.

(2) Preparation of Standard Sample (Sample Immediately after Reaction)

[0147] First, 245 μ L of a 0.1 mol/L phosphate buffer (pH 7.4) containing an NADPH-Co-Factor (BD-Bioscience) , and 1 mg/mL of human hepatic microsome was added to a reaction vessel that had been heated to 37°C with a water bath, and the solution was preincubated for 5 min. To this solution was added 5 μ L of the subject substance solution to start a reaction (final concentration of 1 μ mol/L). Immediately after the reaction was started, 20 μ L of the reaction solution was collected, and added to 180 μ L of acetonitrile (containing candesartan as an internal standard) to quench the reaction. The quenched solution (20 μ L; a sample solution immediately after the reaction) was stirred with 50% acetonitrile (180 μ L) on a deproteinization filter plate, and subjected to suction filtration. The filtrate was then obtained as a standard sample.

(3) Preparation of Reaction Sample (sample after 60 min from Reaction)

[0148] The reaction solution was incubated at 37°C for 60 min, and 20 μ L of the reaction solution was collected, and added to 180 μ L of acetonitrile (containing candesartan as an internal standard) to quench the reaction. The quenched solution (20 μ L; a sample solution after 60 minutes of reaction) was stirred with 50% acetonitrile (180 μ L) on a deproteinization filter plate, and subjected to suction filtration. The filtrate was then obtained as a reaction sample.

(4) Evaluation Method

[0149] Using peak areas from LC-MS/MS, the subject substance remaining rate (%) was calculated from the mass (X) of the subject substance in the standard sample, and the mass (Y) of the subject substance in the reaction sample, according to the following formula.

$$\text{Remaining rate (\%)} = (Y/X) \times 100$$

X: Mass of the subject substance in standard sample (ratio = peak area of subject substance/peak area of internal standard)

Y: Mass of the subject substance in reaction sample (ratio = peak area of subject substance/peak area of internal standard)

(5) Result

[0150] The present compound was shown to have high stability against human hepatic microsome (high remaining rate (%)). As examples, Table 2 below shows the remaining rates of some compounds. The remaining rate was 35% for the compound in Example 6-117 of WO2003/016254.

Table 2

Example	Remaining rate (%)
Comp. Ex. 1	94
Comp. Ex. 2-2	97

(continued)

Example	Remaining rate (%)
Example 2	100

Pharmacological Experiment Example 3: Anti-Tumor Effect in Allograft Model of Mouse Colorectal Cancer Cell Line CT26

[0151] The anti-tumor effect of the present compound was evaluated in an allograft model of the mouse colorectal cancer cell line CT26. CT26 was cultured in a CO₂ incubator, using an RPMI-1640 medium containing 10 vol% inactivated fetal bovine serum (FBS), 100 units/mL of penicillin, and 100 µg/mL of streptomycin. On the day of transplant, CT26 was harvested after removing the culture supernatant, and washing the cells with phosphate buffer (hereinafter, "PBS"). The harvested CT26 cells were suspended in Hank's buffer to obtain transplant cells. The transplant cells (3×10^5) were then subcutaneously transplanted to the right back of a female Balb/C mouse (Charles River Laboratories Japan Inc.) under anesthesia. The present compound was orally administered in a dose of 10 mg/kg, once on the day of transplant, and twice a day from the next day. For the control group, distilled water was administered for the same duration as in the present compound-administered group. The tumor volume (mm³) was determined by calculating a relative tumor volume from the measured tumor lengths along the minor axis and major axis using a digital caliper, according to the following formulae 1 and 2.

$$\text{Tumor volume} = [(\text{minor axis})^2 \times \text{major axis}] / 2$$

[0152] Relative tumor volume = medium value of tumor volumes of each group after 21 days from transplant / medium value of tumor volume of control group after 21 days from transplant

[0153] The present compound had a tumor growth inhibitory effect. FIG. 1 shows the relative tumor volumes for Comparative Example 2-2 and Example 2.

Preparation Examples

Preparation Example 1 (Reference)

[0154] The following components were mixed and punched using an ordinary method to obtain 10,000 tablets containing 10 mg of the active component per tablet.

4-[4-Cyano-2-({[(2'R,4S)-6-(methylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid: 100 g
Carboxymethyl cellulose calcium (disintegrator): 20 g
Magnesium stearate (lubricant): 10 g
Microcrystalline cellulose: 870 g

Preparation Example 2 (Reference)

[0155] The following components were mixed using an ordinary method, and filtered through a dust filter. The preparation was charged into ampules in 5-ml portions, and heat sterilized with an autoclave to obtain 10,000 ampules containing 20 mg of the active component per ampule.

4-[4-Cyano-2-({[(2'R,4S)-6-(methylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid: 200 g
Mannitol: 20 g
Distilled water: 50 L

INDUSTRIAL APPLICABILITY

[0156] The present compound has antagonistic activity against the EP₄ receptor, and is effective for the prevention and/or treatment of diseases caused by EP₄ receptor activation.

Claims

1. A compound selected from 4-[4-cyano-2-({[(2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid, a salt thereof, and a solvate thereof.
2. The compound of claim 1, which is 4-[4-cyano-2-({[(2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid.
3. A pharmaceutical composition comprising the compound of claim 1 as an active ingredient.
4. The composition according to claim 3, which is an EP₄ receptor antagonist.
5. The composition according to claim 3, which is a preventive and/or a therapeutic agent against a disease caused by EP₄ receptor activation.
6. The composition according to claim 5, wherein the disease caused by EP₄ receptor activation is a bone disease, a cancer, a systemic granulomatous disease, an immune disease, alveolar pyorrhea, gingivitis, periodontitis, Kawasaki disease, multiple organ failure, chronic headache, pain, vasculitis, venous incompetence, varicose veins, aneurysm, aortic aneurysm, anal fistula, diabetes insipidus, patent ductus arteriosus in neonates, or cholelithiasis.
7. The composition according to claim 5, wherein the disease caused by EP₄ receptor activation is a cancer.
8. The composition according to claim 7, wherein the cancer is breast cancer, ovarian cancer, colorectal cancer, lung cancer, prostate cancer, head and neck cancer, lymphoma, uveal melanoma, thymoma, mesothelioma, esophageal cancer, stomach cancer, duodenal cancer, hepatocellular carcinoma, cholangiocarcinoma, gallbladder cancer, pancreatic cancer, renal cell carcinoma, renal pelvis and ureter cancer, bladder cancer, penile cancer, testicular cancer, uterus cancer, vaginal cancer, vulvar cancer, skin cancer, malignant bone tumor, soft tissue sarcoma, chondrosarcoma, leukemia, myelodysplastic syndrome, or multiple myeloma.
9. A medicament comprising the compound of claim 1 and at least one selected from an alkylating agent, an antineoplastic, an anti-cancer antibiotic, a plant-based preparation, a hormonal agent, a platinum compound, a topoisomerase inhibitor, a kinase inhibitor, an anti-CD20 antibody, an anti-HER2 antibody, an anti-EGFR antibody, an anti-VEGF antibody, a proteasome inhibitor, an HDAC inhibitor, and an immunomodulator.
10. The compound of claim 1 for use in the prevention and/or treatment of a disease caused by EP₄ receptor activation.
11. The compound for use according to claim 10, wherein the disease caused by EP₄ receptor activation is a bone disease, a cancer, a systemic granulomatous disease, an immune disease, alveolar pyorrhea, gingivitis, periodontitis, Kawasaki disease, multiple organ failure, chronic headache, pain, vasculitis, venous incompetence, varicose veins, aneurysm, aortic aneurysm, anal fistula, diabetes insipidus, patent ductus arteriosus in neonates, or cholelithiasis.
12. The compound for use according to claim 10, wherein the disease caused by EP₄ receptor activation is a cancer.
13. The compound for use according to claim 12, wherein the cancer is breast cancer, ovarian cancer, colorectal cancer, lung cancer, prostate cancer, head and neck cancer, lymphoma, uveal melanoma, thymoma, mesothelioma, esophageal cancer, stomach cancer, duodenal cancer, hepatocellular carcinoma, cholangiocarcinoma, gallbladder cancer, pancreatic cancer, renal cell carcinoma, renal pelvis and ureter cancer, bladder cancer, penile cancer, testicular cancer, uterus cancer, vaginal cancer, vulvar cancer, skin cancer, malignant bone tumor, soft tissue sarcoma, chondrosarcoma, leukemia, myelodysplastic syndrome, or multiple myeloma.

Patentansprüche

1. Verbindung, ausgewählt aus 4-[4-Cyano-2-({[(2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromen-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butansäure, einem Salz davon und einem Solvat davon.
2. Verbindung nach Anspruch 1, bei der es sich um 4-[4-Cyano-2-({[(2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromen-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butansäure handelt.

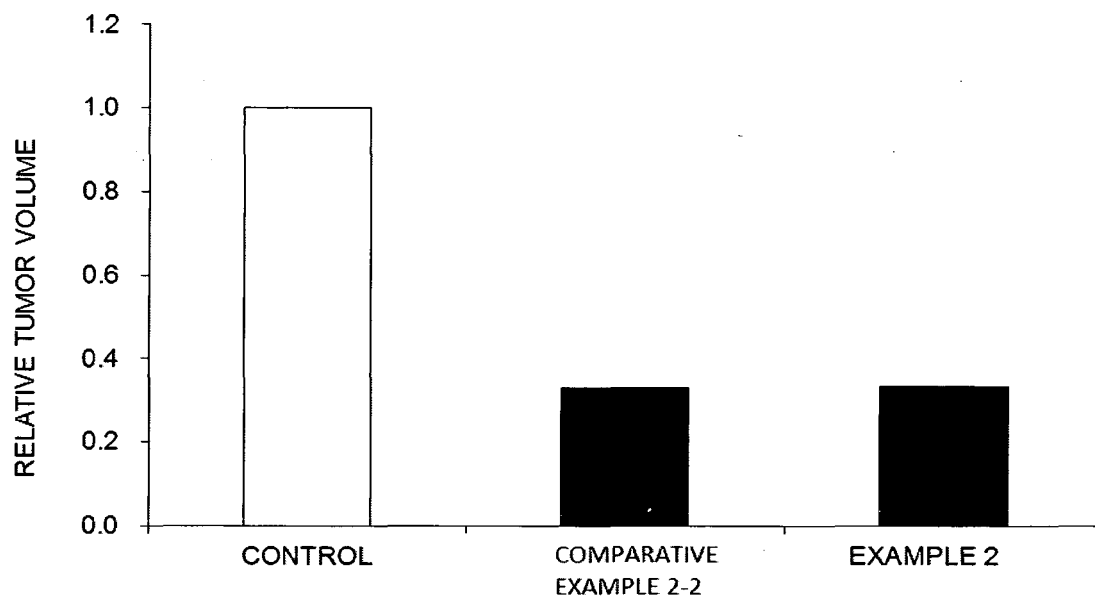
3. Pharmazeutische Zusammensetzung, umfassend die Verbindung nach Anspruch 1 als Wirkstoff.
4. Zusammensetzung gemäß Anspruch 3, bei der es sich um einen EP₄-Rezeptorantagonisten handelt.
- 5 5. Zusammensetzung gemäß Anspruch 3, bei der es sich um ein vorbeugendes und/oder therapeutisches Mittel gegen eine durch EP₄-Rezeptoraktivierung verursachte Erkrankung handelt.
6. Zusammensetzung gemäß Anspruch 5, wobei es sich bei der durch EP₄-Rezeptoraktivierung verursachten Erkrankung um eine Knochenerkrankung, eine Krebserkrankung, eine systemische granulomatöse Erkrankung, eine Im-
10 munerkrankung, Alveolarpyorrhoe, Gingivitis, Parodontitis, Kawasaki-Syndrom, Multiorganversagen, chronischen Kopfschmerz, Schmerz, Vaskulitis, Veneninsuffizienz, Krampfadern, Aneurysma, Aortenaneurysma, Analfistel, Diabetes insipidus, persistierenden Ductus arteriosus bei Neugeborenen oder Cholelithiasis handelt.
7. Zusammensetzung gemäß Anspruch 5, wobei es sich bei der durch EP₄-Rezeptoraktivierung verursachten Erkrankung
15 um eine Krebserkrankung handelt.
8. Zusammensetzung gemäß Anspruch 7, wobei es sich bei der Krebserkrankung um Brustkrebs, Eierstockkrebs, Kolorektalkrebs, Lungenkrebs, Prostatakrebs, Kopf-Hals-Krebs, Lymphom, uveales Melanom, Thymom, Mesotheliom, Speiseröhrenkrebs, Magenkrebs, Zwölffingerdarmkrebs, hepatozelluläres Karzinom, Cholangiokarzinom, Gal-
20 lenblasenkrebs, Pankreaskrebs, Nierenzellkarzinom, Nierenbecken- und Harnleiterkrebs, Blasenkrebs, Peniskrebs, Hodenkrebs, Gebärmutterkrebs, Vaginalkrebs, Vulvakrebs, Hautkrebs, bösartigen Knochentumor, Weichgewebssarkom, Chondrosarkom, Leukämie, myelodysplastisches Syndrom oder multiples Myelom handelt.
9. Medikament, umfassend die Verbindung nach Anspruch 1 und mindestens eines, ausgewählt aus einem Alkylierungsmittel, einem Antimetaboliten, einem Antikrebs-Antibiotikum, einem pflanzlichen Präparat, einem Hormonmittel, einer Platinverbindung, einem Topoisomerase-Inhibitor, einem Kinase-Inhibitor, einem Anti-CD20-Antikörper, einem Anti-HER2-Antikörper, einem Anti-EGFR-Antikörper, einem Anti-VEGF-Antikörper, einem Proteasom-Inhibitor, einem HDAC-Inhibitor und einem Immunmodulator.
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10. Verbindung nach Anspruch 1 zur Verwendung bei der Vorbeugung und/oder Behandlung einer durch EP₄-Rezeptoraktivierung verursachten Erkrankung.
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11. Verbindung zur Verwendung gemäß Anspruch 10, wobei es sich bei der durch EP₄-Rezeptoraktivierung verursachten Erkrankung um eine Knochenerkrankung, eine Krebserkrankung, eine systemische granulomatöse Erkrankung, eine Immunerkrankung, Alveolarpyorrhoe, Gingivitis, Parodontitis, Kawasaki-Syndrom, Multiorganversagen, chronischen Kopfschmerz, Schmerz, Vaskulitis, Veneninsuffizienz, Krampfadern, Aneurysma, Aortenaneurysma, Analfistel, Diabetes insipidus, persistierenden Ductus arteriosus bei Neugeborenen oder Cholelithiasis handelt.
35
12. Verbindung zur Verwendung gemäß Anspruch 10, wobei es sich bei der durch EP₄-Rezeptoraktivierung verursachten Erkrankung um eine Krebserkrankung handelt.
40
13. Verbindung zur Verwendung gemäß Anspruch 12, wobei es sich bei der Krebserkrankung um Brustkrebs, Eierstockkrebs, Kolorektalkrebs, Lungenkrebs, Prostatakrebs, Kopf-Hals-Krebs, Lymphom, uveales Melanom, Thymom, Mesotheliom, Speiseröhrenkrebs, Magenkrebs, Zwölffingerdarmkrebs, hepatozelluläres Karzinom, Cholangiokarzinom, Gallenblasenkrebs, Pankreaskrebs, Nierenzellkarzinom, Nierenbecken- und Harnleiterkrebs, Blasenkrebs, Peniskrebs, Hodenkrebs, Gebärmutterkrebs, Vaginalkrebs, Vulvakrebs, Hautkrebs, bösartigen Knochentumor, Weichgewebssarkom, Chondrosarkom, Leukämie, myelodysplastisches Syndrom oder multiples Myelom handelt.
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Revendications

1. Composé choisi parmi l'acide 4-[4-cyano-2-({(2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromène-4,1'-cyclopropan]-2'-yl)carbonyl}amino)phényl]butanoïque, un sel de celui-ci, et un solvate de celui-ci.
- 55 2. Composé de la revendication 1, qui est l'acide 4-[4-cyano-2-({(2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromène-4,1'-cyclopropan]-2'-yl)carbonyl}amino)phényl]butanoïque.
3. Composition pharmaceutique comprenant le composé de la revendication 1 en tant qu'ingrédient actif.

4. Composition selon la revendication 3, qui est un antagoniste du récepteur EP₄.
5. Composition selon la revendication 3, qui est un agent préventif et/ou thérapeutique contre une maladie causée par une activation du récepteur EP₄.
6. Composition selon la revendication 5, où la maladie causée par l'activation du récepteur EP₄ est une maladie osseuse, un cancer, une granulomatose systémique, une maladie immunitaire, la pyorrhée alvéolo-dentaire, la gingivite, la parodontite, la maladie de Kawasaki, la défaillance multiviscérale, les maux de tête chroniques, la douleur, la vascularite, l'incompétence du réseau veineux, les varices, l'anévrisme, l'anévrisme de l'aorte, la fistule anale, le diabète insipide, la persistance du canal artériel chez le nouveau-né, ou la cholélithiase.
7. Composition selon la revendication 5, où la maladie causée par l'activation du récepteur EP₄ est un cancer.
8. Composition selon la revendication 7, où le cancer est le cancer du sein, le cancer de l'ovaire, le cancer colorectal, le cancer du poumon, le cancer de la prostate, le cancer de la tête et du cou, le lymphome, le mélanome uvéal, le thymome, le mésothéliome, le cancer de l'œsophage, le cancer de l'estomac, le cancer du duodénum, le carcinome hépatocellulaire, le cholangiocarcinome, le cancer de la vésicule biliaire, le cancer pancréatique, le carcinome à cellules rénales, le cancer du bassinet et de l'uretère, le cancer de la vessie, le cancer du pénis, le cancer du testicule, le cancer de l'utérus, le cancer du vagin, le cancer de la vulve, le cancer de la peau, les tumeurs osseuses malignes, le sarcome des tissus mous, le chondrosarcome, la leucémie, le syndrome myélodysplasique, ou le myélome multiple.
9. Médicament comprenant le composé de la revendication 1 et au moins un sélectionné parmi un agent alkylant, un antimétabolite, un antibiotique anticancéreux, une préparation à base de plantes, un agent hormonal, un composé de platine, un inhibiteur de topoisomérase, un inhibiteur de kinase, un anticorps anti-CD20, un anticorps anti-HER2, un anticorps anti-EGFR, un anticorps anti-VEGF, un inhibiteur du protéasome, un inhibiteur de HDAC, et un immunomodulateur.
10. Composé de la revendication 1 pour utilisation dans la prévention et/ou le traitement d'une maladie causée par une activation du récepteur EP₄.
11. Composé pour utilisation selon la revendication 10, où la maladie causée par l'activation du récepteur EP₄ est une maladie osseuse, un cancer, une granulomatose systémique, une maladie immunitaire, la pyorrhée alvéolo-dentaire, la gingivite, la parodontite, la maladie de Kawasaki, la défaillance multiviscérale, les maux de tête chroniques, la douleur, la vascularite, l'incompétence du réseau veineux, les varices, l'anévrisme, l'anévrisme de l'aorte, la fistule anale, le diabète insipide, la persistance du canal artériel chez le nouveau-né, ou la cholélithiase.
12. Composé pour utilisation selon la revendication 10, où la maladie causée par l'activation du récepteur EP₄ est un cancer.
13. Composé pour utilisation selon la revendication 12, où le cancer est le cancer du sein, le cancer de l'ovaire, le cancer colorectal, le cancer du poumon, le cancer de la prostate, le cancer de la tête et du cou, le lymphome, le mélanome uvéal, le thymome, le mésothéliome, le cancer de l'œsophage, le cancer de l'estomac, le cancer du duodénum, le carcinome hépatocellulaire, le cholangiocarcinome, le cancer de la vésicule biliaire, le cancer pancréatique, le carcinome à cellules rénales, le cancer du bassinet et de l'uretère, le cancer de la vessie, le cancer du pénis, le cancer du testicule, le cancer de l'utérus, le cancer du vagin, le cancer de la vulve, le cancer de la peau, les tumeurs osseuses malignes, le sarcome des tissus mous, le chondrosarcome, la leucémie, le syndrome myélodysplasique, ou le myélome multiple.

FIG. 1



REFERENCES CITED IN THE DESCRIPTION

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