such as age-related maculopathy or diabetic retinopathy.

[0009] In addition, there is no report proposing use of an S1P receptor agonist for an ophthalmic disease with attention focused on its barrier function-enhancing action between vascular endothelial cells. Some of the inventors of the present invention previously proposed an invention in which an S1P receptor agonist was used for treatment of cerebral aneurysm (Patent Literature 4). It was shown that the treatment was achieved because, as its action, the S1P receptor agonist reduced permeability of vascular endothelial cells to decrease the number of macrophages infiltrating cerebral aneurysm walls. However, there is no description that the S1P receptor agonist can be applied to an ophthalmic disease.

Citation List

Patent Literature

[0010] [PTL 1] WO 2005/002559 A2

[PTL 2] WO 2007/116866 A1

[PTL 3] WO 2010/064707 A1

[PTL 4] WO 2014/175287 A1

Summary

Technical Problem

[0011] There is provided a pharmaceutical useful for preventing or treating an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular

permeability.

Solution to Problem

[0012] The inventors of the present disclosure have made investigations as to whether an S1P receptor agonist can be used for preventing or treating an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability, with attention focused particularly on enhancing a barrier function between vascular endothelial cells, and as a result, have found that the desired object is achieved by a compound having a specific S1P receptor agonist activity profile.

[0013] That is, the inventors have made extensive investigations on a selective S1P receptor agonist having agonist activity at an $S1P_1$ receptor, and as a result, have found that the selective S1P receptor agonist is effective for an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability. Thus, the inventors have completed the present disclosure.

[0014] The present disclosure relates to a pharmaceutical for preventing or treating an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability, the pharmaceutical including as an active ingredient a selective S1P receptor agonist, that is, a compound that has agonist activity at an $S1P_1$ receptor, and that may further have agonist activity at one or both of an $S1P_4$ receptor and an $S1P_5$

receptor, or a pharmaceutically acceptable salt thereof.

[0015] The present disclosure also relates to a pharmaceutical composition for preventing or treating an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability, the pharmaceutical composition including a selective S1P receptor agonist and a pharmaceutically acceptable excipient. The pharmaceutical composition encompasses a preventive or therapeutic agent for an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability, the preventive or therapeutic agent including a selective S1P receptor agonist.

[0015a] In one aspect, the present disclosure refers to a pharmaceutical composition for preventing or treating an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability, the pharmaceutical composition comprising as an active ingredient a selective S1P receptor agonist having agonist activity at an $S1P_1$ receptor.

[0016] The present disclosure also relates to: a use of a selective S1P receptor agonist for manufacture of a pharmaceutical composition for preventing or treating an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability; a use of a selective S1P receptor agonist for preventing or treating an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability; a selective S1P receptor agonist

for use in prevention or treatment of an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability; and a method of preventing or treating an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability, the method including administering an effective dose of a selective S1P receptor

agonist to a subject. The term "subject" refers to a human or any other animal in need of the prevention or treatment, and in one example, refers to a human in need of the prevention or treatment.

[0016a] In another aspect, the present disclosure refers to use of an effective dose of a selective S1P receptor agonist having agonist activity at an $S1P_1$ receptor in the manufacture of a medicament for preventing or treating an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability in a subject.

[0016b] In another aspect, the present disclosure refers to a selective S1P receptor agonist having agonist activity at an $S1P_1$ receptor, for use in prevention or treatment of an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability.

[0017] That is, the present disclosure includes the following items.

(1) A pharmaceutical composition for preventing or treating an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability, the pharmaceutical composition including as an active ingredient a selective S1P receptor agonist having agonist activity at an $S1P_1$ receptor.

(2) The pharmaceutical composition according to Item (1), wherein the selective S1P receptor agonist is a compound having $S1P_1$ receptor

agonist activity and further having agonist activity at one or both of an $S1P_5$ receptor and an $S1P_4$ receptor, or a pharmaceutically acceptable salt thereof.

(3) The pharmaceutical composition according to Item (1), wherein the selective S1P receptor agonist is a compound having $S1P_1$ receptor agonist activity and further having agonist activity at an $S1P_5$ receptor, or a pharmaceutically acceptable salt thereof.

(4) The pharmaceutical composition according to any one of Items (1) to (3), wherein the selective S1P receptor agonist is a compound or a pharmaceutically acceptable salt thereof selected from the group consisting of:

5-{5-[3-(trifluoromethyl)-4-{[(2S)-1,1,1-trifluoropropan-2-yl]

Claims

[Claim 1] A pharmaceutical composition for preventing or treating an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability, the pharmaceutical composition comprising as an active ingredient a selective S1P receptor agonist having agonist activity at an $S1P_1$ receptor.

[Claim 2] The pharmaceutical composition according to claim 1, wherein the selective S1P receptor agonist is a compound having $S1P_1$ receptor agonist activity and further having agonist activity at one or both of an $S1P_5$ receptor and an $S1P_4$ receptor, or a pharmaceutically acceptable salt thereof.

[Claim 3] The pharmaceutical composition according to claim 1, wherein the selective S1P receptor agonist is a compound having $S1P_1$ receptor agonist activity and further having agonist activity at an $S1P_5$ receptor, or a pharmaceutically acceptable salt thereof.

[Claim 4] The pharmaceutical composition according to any one of claims 1 to 3, wherein the selective S1P receptor agonist is a compound or a pharmaceutically acceptable salt thereof selected from the group consisting of:
5-{5-[3-(trifluoromethyl)-4-{[(2S)-1,1,1-trifluoropropan-2-yl]oxy}phenyl]-1,2,4-oxadiazol-3-yl}-1H-benzimidazole or a

pharmaceutically acceptable salt thereof; 1-[(7-{[4-(2,2,2-trifluoroethoxy)-3-(trifluoromethyl)phenyl]methoxy}-2H-1-benzopyran-3-yl)methyl]piperidine-4-carboxylic acid or a pharmaceutically acceptable salt thereof; 1-({4-[(1E)-N-{[4-cyclohexyl-3-(trifluoromethyl)phenyl]methoxy}ethanimidoyl]-2-ethylphenyl}methyl)azetidine-3-carboxylic acid or a pharmaceutically acceptable salt thereof; 5-(3-{(1S)-1-[(2-hydroxyethyl)amino]-2,3-dihydro-1H-inden-4-yl}-1,2,4-oxadiazol-5-yl)-2-[(propan-2-yl)oxy]benzonitrile or a pharmaceutically acceptable salt thereof; (2Z,5Z)-5-({3-chloro-4-[(2R)-2,3-dihydroxypropoxy]phenyl}methylidene)-3-(2-methylphenyl)-2-(propylimino)-1,3-thiazolidin-4-one or a pharmaceutically acceptable salt thereof; [(3R)-7-{[4-cyclopentyl-3-(trifluoromethyl)phenyl]methoxy}-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl]acetic acid or a pharmaceutically acceptable salt thereof; and 2-amino-2-[2-(4-{[3-(benzyloxy)phenyl]sulfanyl}-2-chlorophenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable salt thereof.

[Claim 5] The pharmaceutical composition according to claim 4, wherein the selective S1P receptor agonist is 5-{5-[3-(trifluoromethyl)-4-{[(2S)-1,1,1-trifluoropropan-2-yl]oxy}phenyl]-1,2,4-oxadiazol-3-yl}-1H-benzimidazole or a pharmaceutically acceptable salt thereof.

[Claim 6] The pharmaceutical composition according to any one of claims 1 to 5, wherein the ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability is exudative age-related macular degeneration, diabetic retinopathy, diabetic macular edema, retinopathy of prematurity, myopic choroidal neovascularization, secondary choroidal neovascularization, retinal artery occlusion, retinal vein occlusion, neovascular glaucoma, retinitis pigmentosa, or edema caused by retinal photocoagulation.

[Claim 7] The pharmaceutical composition according to any one of claims 1 to 5, wherein the ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability is exudative age-related macular degeneration, diabetic retinopathy, diabetic macular edema, myopic choroidal neovascularization, retinal artery occlusion, retinal vein occlusion, or neovascular glaucoma.

[Claim 8] The pharmaceutical composition according to any one of claims 1 to 7, wherein the pharmaceutical composition is to be intraocularly injected or intravitreally injected to treat the ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability.

[Claim 9] The pharmaceutical composition according to claim 8, wherein the pharmaceutical composition is to be intravitreally injected to treat the ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability.

[Claim 10] Use of an effective dose of a selective S1P receptor agonist having agonist activity at an $S1P_1$ receptor in the manufacture of a medicament for preventing or treating an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability in a subject.

[Claim 11] The use according to claim 10, wherein the selective S1P receptor agonist is a compound having $S1P_1$ receptor agonist activity and further having agonist activity at one or both of an $S1P_5$ receptor and an $S1P_4$ receptor, or a pharmaceutically acceptable salt thereof.

[Claim 12] The use according to claim 10, wherein the selective S1P receptor agonist is a compound having $S1P_1$ receptor agonist activity and further having agonist activity at an $S1P_5$ receptor, or a pharmaceutically acceptable salt thereof.

[Claim 13] The use according to any one of claims 10 to 12, wherein the selective S1P receptor agonist is a compound or a pharmaceutically acceptable salt thereof selected from the group consisting of:

5-{5-[3-(trifluoromethyl)-4-{[(2S)-1,1,1-trifluoropropan-2-yl]oxy}phenyl]-1,2,4-oxadiazol-3-yl}-1H-benzimidazole or a pharmaceutically acceptable salt thereof;

1-[(7-{[4-(2,2,2-trifluoroethoxy)-3-(trifluoromethyl)phenyl]methoxy}-2H-1-benzopyran-3-yl)methyl]piperidine-4-carboxylic acid or a pharmaceutically acceptable salt thereof;

1-({4-[(1E)-N-{[4-cyclohexyl-3-(trifluoromethyl)phenyl]methoxy}ethanimidoyl]-2-ethylphenyl}methyl)azetidine-3-carboxylic acid or a pharmaceutically acceptable salt thereof;

5-(3-{(1S)-1-[(2-hydroxyethyl)amino]-2,3-dihydro-1H-inden-4-yl}-1,2,4-oxadiazol-5-yl)-2-[(propan-2-yl)oxy]benzonitrile or a pharmaceutically acceptable salt thereof;

(2Z,5Z)-5-({3-chloro-4-[(2R)-2,3-dihydroxypropoxy]phenyl}methylidene)-3-(2-methylphenyl)-2-(propylimino)-1,3-thiazolidin-4-one or a pharmaceutically acceptable salt thereof;

[(3R)-7-{[4-cyclopentyl-3-(trifluoromethyl)phenyl]methoxy}-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl]acetic acid or a pharmaceutically acceptable salt thereof; and

2-amino-2-[2-(4-{[3-(benzyloxy)phenyl]sulfanyl}-2-chlorophenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable salt thereof.

[Claim 14] The use according to claim 13, wherein the selective S1P receptor agonist is

5-{5-[3-(trifluoromethyl)-4-{[(2S)-1,1,1-trifluoropropan-2-yl]o

xy}phenyl]-1,2,4-oxadiazol-3-yl}-1H-benzimidazole or a pharmaceutically acceptable salt thereof.

[Claim 15] The use according to any one of claims 10 to 14, wherein the ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability is exudative age-related macular degeneration, diabetic retinopathy, diabetic macular edema, retinopathy of prematurity, myopic choroidal neovascularization, secondary choroidal neovascularization, retinal artery occlusion, retinal vein occlusion, neovascular glaucoma, retinitis pigmentosa, or edema caused by retinal photocoagulation.

[Claim 16] The use according to any one of claims 10 to 14, wherein the ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability is exudative age-related macular degeneration, diabetic retinopathy, diabetic macular edema, myopic choroidal neovascularization, retinal artery occlusion, retinal vein occlusion, or neovascular glaucoma.

[Claim 17] The use according to any one of claims 10 to 16, wherein the medicament is to be administered via intraocular injection or intravitreal injection.

[Claim 18] The use according to claim 17, wherein the medicament is to be administered via intravitreal injection.

[Claim 19] A selective S1P receptor agonist having agonist activity at an $S1P_1$ receptor, for use in prevention or treatment of an ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability.

[Claim 20] The selective S1P receptor agonist for use according to claim 19, wherein the selective S1P receptor agonist is a compound having $S1P_1$ receptor agonist activity and further having agonist activity at one or both of an $S1P_5$ receptor and an $S1P_4$ receptor, or a pharmaceutically acceptable salt thereof.

[Claim 21] The selective S1P receptor agonist for use according to claim 19, wherein the selective S1P receptor agonist is a compound having $S1P_1$ receptor agonist activity and further having agonist activity at an $S1P_5$ receptor, or a pharmaceutically acceptable salt thereof.

[Claim 22] The selective S1P receptor agonist for use according to any one of claims 19 to 21, wherein the selective S1P receptor agonist is a compound or a pharmaceutically acceptable salt thereof selected from the group consisting of:

5-{5-[3-(trifluoromethyl)-4-{[(2S)-1,1,1-trifluoropropan-2-yl]o

xy}phenyl]-1,2,4-oxadiazol-3-yl}-1H-benzimidazole or a pharmaceutically acceptable salt thereof; 1-[(7-{[4-(2,2,2-trifluoroethoxy)-3-(trifluoromethyl)phenyl]methoxy}-2H-1-benzopyran-3-yl)methyl]piperidine-4-carboxylic acid or a pharmaceutically acceptable salt thereof; 1-({4-[(1E)-N-{[4-cyclohexyl-3-(trifluoromethyl)phenyl]methoxy}ethanimidoyl]-2-ethylphenyl}methyl)azetidine-3-carboxylic acid or a pharmaceutically acceptable salt thereof; 5-(3-{(1S)-1-[(2-hydroxyethyl)amino]-2,3-dihydro-1H-inden-4-yl}-1,2,4-oxadiazol-5-yl)-2-[(propan-2-yl)oxy]benzonitrile or a pharmaceutically acceptable salt thereof; (2Z,5Z)-5-({3-chloro-4-[(2R)-2,3-dihydroxypropoxy]phenyl}methylidene)-3-(2-methylphenyl)-2-(propylimino)-1,3-thiazolidin-4-one or a pharmaceutically acceptable salt thereof; [(3R)-7-{[4-cyclopentyl-3-(trifluoromethyl)phenyl]methoxy}-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl]acetic acid or a pharmaceutically acceptable salt thereof; and 2-amino-2-[2-(4-{[3-(benzyloxy)phenyl]sulfanyl}-2-chlorophenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable salt thereof.

[Claim 23] The selective S1P receptor agonist for use according to claim 22, wherein the selective S1P receptor agonist is 5-{5-[3-(trifluoromethyl)-4-{[(2S)-1,1,1-trifluoropropan-2-yl]oxy}phenyl]-1,2,4-oxadiazol-3-yl}-1H-benzimidazole or a

pharmaceutically acceptable salt thereof.

[Claim 24] The selective S1P receptor agonist for use according to any one of claims 19 to 23, wherein the ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability is exudative age-related macular degeneration, diabetic retinopathy, diabetic macular edema, retinopathy of prematurity, myopic choroidal neovascularization, secondary choroidal neovascularization, retinal artery occlusion, retinal vein occlusion, neovascular glaucoma, retinitis pigmentosa, or edema caused by retinal photocoagulation.

[Claim 25] The selective S1P receptor agonist for use according to any one of claims 19 to 23, wherein the ophthalmic disease associated with intraocular neovascularization and/or increased intraocular vascular permeability is exudative age-related macular degeneration, diabetic retinopathy, diabetic macular edema, myopic choroidal neovascularization, retinal artery occlusion, retinal vein occlusion, or neovascular glaucoma.

[Claim 26] The selective S1P receptor agonist for use according to any one of claims 19 to 25, wherein the selective S1P receptor agonist is for use in intraocular injection or intravitreal injection.

[Claim 27] The selective S1P receptor agonist for use according to

claim 26, wherein the selective S1P receptor agonist is for use in intravitreal injection.