diseases such as cancer, rheumatoid arthritis, age-related macular degeneration, diabetic retinopathy and diabetic macular edema, etc.

[0003] Also, in Patent Document 2, there are disclosed a benzenesulfonic acid salt of 2-[[[2-[(hydroxyacetyl)amino]-4-pyridinyl]methyl]thio]-N-[4-(trifluoromethoxy)-phenyl]-3-pyridinecarboxamide, which is one of the compound represented by the formula (1), crystal thereof, crystal polymorphism thereof and processes for producing these. In addition, it has also been disclosed that a benzenesulfonic acid salt of 2-[[[2-[(hydroxyacetyl)amino]-4-pyridinyl]methyl]thio]-N-[4-(trifluoromethoxy)phenyl]-3-pyridinecarboxamide is excellent in storage stability, and no deposition of minerals is recognized in the stomach even when repeated oral administration is carried out.

[0004] On the other hand, in Patent Documents 3 to 5, there are disclosed a composition for ophthalmology containing N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea which is a compound inhibiting receptor tyrosine kinase and polyethylene glycol.

[0005] Further, in Patent Document 6, a composition for ophthalmology containing rapamycin and polyethylene glycol has been disclosed.

[0006] However, in Patent Documents 1 to 6, a pharmaceutical composition containing a compound represented by the formula (1) or a salt thereof and polyethylene glycol is not disclosed, and it is never disclosed that the polyethylene glycol improves stability of the pharmacologically active compound in the pharmaceutical composition.

PRIOR ART DOCUMENTS

PATENT DOCUMENTS

[0007]

Patent Document 1: US Patent Application Publication No. 2007/0149574A
Patent Document 2: US Patent Application Publication No. 2012/0116088A
Patent Document 3: WO 2007/076358A
Patent Document 4: WO2009/014510A
Patent Document 5: WO2010/101971A
Patent Document 6: US Patent No. 8,367,097

SUMMARY OF INVENTION

TECHNICAL PROBLEM

[0008] The present inventors have found that, in the development stage of a pharmaceutical composition containing the compound represented by the above-mentioned formula (1) or a salt thereof (in the following, it is also referred to as "the

present compound"), stability of the present compound is remarkably lowered in a pharmaceutical composition in which the present compound is being dissolved.

[0009] An object of the present invention is to provide a pharmaceutical composition in which the pharmaceutical composition contains the present compound, the present compound in the pharmaceutical composition is stable, and the pharmaceutical composition sustains release of the present compound.

SOLUTION TO PROBLEM

[0010] The present inventors have intensively studied about the solvent (for example, polyethylene glycol, dimethylsulfoxide, N-methylpyrrolidone, N,N-dimethylacetamide) to dissolve the present compound to solve the above-mentioned problems, and as a result, they have found that the present compound in a pharmaceutical composition has high residual ratio under long term storage wherein polyethylene glycol is used for. The present invention has been accomplished.

[0011] That is, the present invention relates to the following.

(1) A pharmaceutical composition comprising a compound represented by the above-mentioned formula (1) or a salt thereof and polyethylene glycol.

(2) The pharmaceutical composition described in the above-mentioned (1), wherein, in the above-mentioned formula (1),

R^1 represents a $C_{1\text{-}6}$ alkoxyl group or a $C_{1\text{-}6}$ alkoxyl group substituted by one or more halogen atoms; and

R^2 represents a $C_{1\text{-}6}$ alkylcarbonyl group or a $C_{1\text{-}6}$ alkylcarbonyl group substituted by one or more hydroxyl groups.

(3) The pharmaceutical composition described in the above-mentioned (1), wherein, in the above-mentioned formula (1),

R^1 represents a $C_{1\text{-}6}$ alkoxyl group substituted by one or more halogen atoms; and

R^2 represents a $C_{1\text{-}6}$ alkylcarbonyl group substituted by one or more hydroxyl groups.

(4) The pharmaceutical composition described in the above-mentioned (1), wherein the compound represented by the above-mentioned formula (1) is 2-[[[2-[(hydroxyacetyl)-amino]-4-pyridinyl]methyl]thio]-N-[4-(trifluoromethoxy)phenyl]-3-pyridine-carboxamide.

(5) The pharmaceutical composition described in the above-mentioned any one of (1) to (4), wherein an average molecular weight of the polyethylene glycol is within the range of 100 to 2,000.

(6) The pharmaceutical composition described in the above-mentioned any one of (1) to

(4), wherein an average molecular weight of the polyethylene glycol is within the range of 200 to 600.

(7) The pharmaceutical composition described in the above-mentioned any one of (1) to (4), wherein the polyethylene glycol is PEG 400.

(8) The pharmaceutical composition described in the above-mentioned any one of (1) to (7), wherein the amount of the polyethylene glycol in the pharmaceutical composition is 70 to 99.99% (w/w).

(9) The pharmaceutical composition described in the above-mentioned any one of (1) to (8), wherein the amount of the compound represented by the above-mentioned formula (1) or a salt thereof is 0.01 to 20% (w/v).

(10) The pharmaceutical composition described in the above-mentioned any one of (1) to (9), wherein it is used for prophylaxis or treatment of an eye disease.

(11) The pharmaceutical composition described in the above-mentioned (10), wherein the eye disease is age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, retinal artery occlusion, polypoidal choroidal vasculopathy, retinal angiomatous proliferation, myopic choroidal neovascularization, diabetic macular edema, ocular tumor, radiation retinopathy, iris rubeosis, neovascular glaucoma or proliferative vitreoretinopathy (PVR).

(12) The pharmaceutical composition described in the above-mentioned (10) or (11), wherein it is for intravitreal administration.

(13) The pharmaceutical composition described in the above-mentioned (12), wherein it is administered with 1 to 100 μL per one time.

(14) The pharmaceutical composition described in the above-mentioned (12) or (13), wherein it is administered with an interval of once a week to once 3 years.

(15) A method for stabilizing the compound represented by the above-mentioned formula (1) or a salt thereof which comprises dissolving the above-mentioned formula (1) or a salt thereof in polyethylene glycol.

(16) The method described in the above-mentioned (15), wherein the compound represented by the above-mentioned formula (1) is 2-[[[2-[(hydroxyacetyl)amino]-4-pyridinyl]methyl]thio]-N-[4-(trifluoromethoxy)phenyl]-3-pyridinecarboxamide.

Further, the present invention relates to the following.

(17) The method described in the above-mentioned (15), wherein, in the above-mentioned formula (1),

R^1 represents a $C_{1\text{-}6}$ alkoxyl group or a $C_{1\text{-}6}$ alkoxyl group substituted by one or more halogen atoms; and

R^2 represents a $C_{1\text{-}6}$ alkylcarbonyl group or a $C_{1\text{-}6}$ alkylcarbonyl group

crystal polymorphs are also included in the scope of the present invention.

[0025] Preferred examples of (a) the compound represented by the formula (1) include a compound in which the respective groups in the formula (1) are the groups shown below, or a salt thereof.

(a1) R^1 represents a C_{1-6} alkoxyl group or a C_{1-6} alkoxyl group substituted by one or more halogen atoms; and/or

(a2) R^2 represents a C_{1-6} alkylcarbonyl group or a C_{1-6} alkylcarbonyl group substituted by one or more hydroxyl groups.

[0026] That is, the compound represented by the formula (1), a compound or a salt thereof comprising one or two or more respective combinations selected from the above-mentioned (a1) and (a2) include as a preferred example(s).

[0027] (b) More preferred example of the compound represented by the formula (1) includes a compound or a salt thereof in which each group in the formula (1) is a group mentioned below.

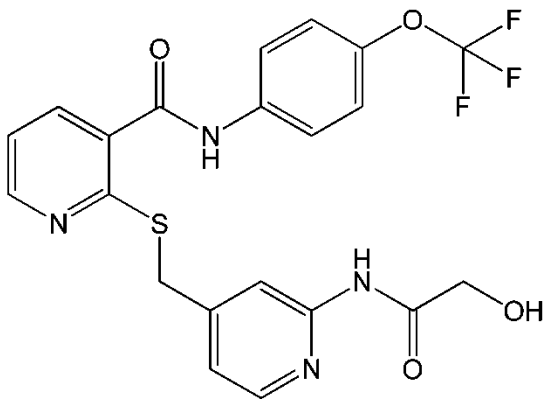
[0028] (b1) R^1 represents a C_{1-6} alkoxyl group substituted by one or more halogen atoms; and/or

(b2) R^2 represents a C_{1-6} alkylcarbonyl group substituted by one or more hydroxyl groups.

[0029] That is, the compound represented by the formula (1) includes a compound comprising 1 or 2 or more combinations selected from the above-mentioned (b1) and (b2) or a salt thereof as a preferred example. Also, the selected conditions may be combined with the conditions of (a).

[0030] Most preferred example of (c) the compound represented by the formula (1) is the compound (2-[[[2-[(hydroxyacetyl)amino]-4-pyridinyl]methyl]-thio]-N-[4-(trifluoromethoxy)phenyl]-3-pyridinecarboxamide) represented by the formula (2):

[Formula 2]



(2)

or a salt thereof.

Stability of the pharmaceutical composition of the present invention was investigated.

[0070] 1-1. Preparation of formulation to be tested

A suitable amount of polyethylene glycol 400 (Nacalai Tesque Inc.) was added to 0.10 g of the compound (2-[[[2-[(hydroxyacetyl)amino]-4-pyridinyl]methyl]thio]-N-[4-(trifluoromethoxy)phenyl]-3-pyridinecarboxamide, in the following, it is also called as Compound A; prepared according to the method described in US Patent Application Publication No. 2007/0149574A) represented by the above-mentioned formula (2), and the whole amount was made 10 mL and dissolved under stirring to prepare a formulation of Example 1.

[0071] In the same manner as in the preparation method of Example 1, formulations of Examples 2 to 4 shown in Table 1 were prepared. The polyethylene glycols used were available from Nacalai Tesque Inc.

[0072] 1-2. Test method

In 3 mL of a glass vial (Wheaton) was filled 0.4 mL of the formulation to be tested, and the amount of 2-[[[2-[(hydroxyacetyl)amino]-4-pyridinyl]methyl]thio]-N-[4-(trifluoromethoxy)phenyl]-3-pyridinecarboxamide when it was preserved at 40°C and 60°C until each 3 months and 4 weeks were determined by using high-performance liquid chromatography (HPLC) to calculate the residual ratio (%) thereof.

[0073] 1-3. Test results and consideration

The test results are shown in Table 1.

[0074]

[Table 1]

			Example 1	Example 2	Example 3	Example 4
Compound A			0.1g	0.1g	0.1g	0.1g
Polyethylene glycol 400			Quantum sufficit	-	-	-
Polyethylene glycol 200			-	Quantum sufficit	-	-
Polyethylene glycol 300			-	-	Quantum sufficit	-
Polyethylene glycol 600			-	-	-	Quantum sufficit
Whole amount			10mL	10mL	10mL	10mL
Residual ratio (%)	60°C	2 weeks	98.7	96.7	98.2	100.3
		4 weeks	93.2	85.8	90.2	96.5
	40°C	1 month	98.4	97.8	98.8	99.1

		2 months	99.6	96.9	98.5	99.3
		3 months	100.2	96.2	95.9	97.6

[0075] As can be clearly seen from Table 1, formulations of Examples 1 to 4 maintained high residual ratio at 40°C for 3 months and at 60°C for 4 weeks. In particular, high residual ratios were shown when polyethylene glycol 400 or polyethylene glycol 600 had been used. From the above, it was confirmed that the compositions of the present invention had excellent stability.

[0076] 2. Stability evaluation test (2)

Stability of the pharmaceutical composition of the present invention was investigated.

[0077] 2-1. Preparation of formulation to be tested

Suitable amount of polyethylene glycol 400 (NOF CORPORATION) was added to 0.6 g or 12 g of Compound A and the whole amount was made 240 mL, and the mixture was dissolved by stirring to prepare formulations of Examples 5 and 6.

[0078] 2-2. Test method

In 3 mL of glass vial (Wheaton) was filled 2 mL of the formulation to be tested, and the amount of 2-[[[2-[(hydroxyacetyl)amino]-4-pyridinyl]methyl]thio]-N-[4-(trifluoromethoxy)phenyl]-3-pyridinecarboxamide when it was preserved at 25°C until each 3 months was determined by using high-performance liquid chromatography (HPLC) to calculate the residual ratio (%) thereof.

[0079] 2-3. Test results and consideration

The test results are shown in Table 2.

[0080]

[Table 2]

		Example 5	Example 6
Compound A		0.6g	12g
Polyethylene glycol 400		Quantum sufficit	Quantum sufficit
Whole amount		240mL	240mL
Residual ratio (%)	25°C, 3 months	93.7	98.3

[0081] As can be clearly seen from Table 2, the formulations of Example 5and 6 maintained high residual ratios at 25°C for 3 months. From the above, it was confirmed that the compositions of the present invention had excellent stability.

[0082] 3. Stability evaluation test (3)

Stabilities of the compositions of the present invention containing

dimethylsulfoxide and a nonionic surfactant were investigated.

[0083] 3-1. Preparation of formulation to be tested

Example 7 shown in Table 3 was prepared by adding 1.50 g of dimethylsulfoxide and 32.11 g of polyethylene glycol 400 to 0.75 g of Compound A, and dissolved by stirring. Also, in the same manner as in the preparation method of Example 1, formulations of Examples 8 and 9 shown in Table 3 were prepared. Polyethylene glycol 400 used was available from NOF CORPORATION, dimethylsulfoxide from Nacalai Tesque Inc., polysorbate 20 from Nikko Chemicals Co., Ltd., and Polyoxyl 35 castor oil from BASF.

[0084] 3-2. Test method

In 2 mL glass vial (Shiotani Glass Co., Ltd.) was filled 0.4 mL of the formulation to be tested, and the amount of 2-[[[2-[(hydroxyacetyl)amino]-4-pyridinyl]-methyl]thio]-N-[4-(trifluoromethoxy)phenyl]-3-pyridinecarboxamide when it was preserved at 60°C until 4 weeks were determined by using high-performance liquid chromatography (HPLC) to calculate the residual ratio (%) thereof.

[0085] 3-3. Test results and consideration

The test results are shown in Table 3.

[0086]

[Table 3]

		Example 7	Example 8	Example 9
Compound A		0.75g	0.38g	0.37g
Dimethylsulfoxide		1.50g	-	-
Polysorbate 20		-	0.75g	-
Polyoxyl 35 castor oil		-	-	0.75g
Polyethylene glycol 400		32.11g	Quantum sufficit	Quantum sufficit
Whole amount		About 30mL	15mL	15mL
Residual ratio (%)	60°C, 4 weeks	84.7	75.9	75.3

[0087] As can be clearly seen from Table 3, the formulations of Examples 7 to 9 maintained high residual ratios at 60°C for 4 weeks. From the above, it was confirmed that the compositions of the present invention had excellent stability even when dimethylsulfoxide or a nonionic surfactant had been added.

[0088] 4. Pharmacokinetics test

Pharmacokinetics after intravitreal administration of the compositions of the present invention were investigated.

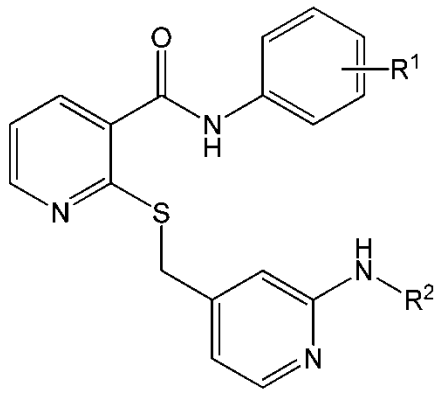
[0089] 4-1. Preparation of formulation to be tested

To 100.5 mg of Compound A was added 1.8 mL of polyethylene glycol 400

CLAIMS

1. A parenteral pharmaceutical composition for prophylaxis or treatment of an eye disease which comprises a compound represented by the formula (1):

~~[Formula 3]~~



(1)

wherein

R^1 represents a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, a C_{1-6} alkyl group substituted by one or more halogen atoms, a C_{1-6} alkoxyl group or a C_{1-6} alkoxyl group substituted by one or more halogen atoms; and

R^2 represents a hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkylcarbonyl group or a C_{1-6} alkylcarbonyl group substituted by one or more hydroxyl groups,

or a salt thereof and polyethylene glycol whose average molecular weight is within the range of 200 to 600,

wherein the compound represented by the formula (1) or the salt thereof is dissolved in the composition.

2. The parenteral pharmaceutical composition according to claim 1, wherein

R^1 represents a C_{1-6} alkoxyl group or a C_{1-6} alkoxyl group substituted by one or more halogen atoms; and

R^2 represents a C_{1-6} alkylcarbonyl group or a C_{1-6} alkylcarbonyl group substituted by one or more hydroxyl groups in the formula (1).

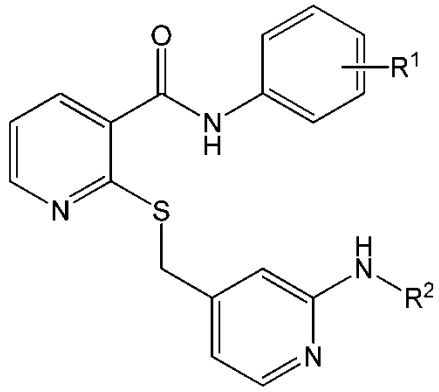
3. The parenteral pharmaceutical composition according to claim 1, wherein

R^1 represents a C_{1-6} alkoxyl group substituted by one or more halogen atoms; and

R^2 represents a C_{1-6} alkylcarbonyl group substituted by one or more hydroxyl groups in the formula (1).

4. The parenteral pharmaceutical composition according to claim 1, wherein the compound represented by the formula (1) is 2-[[[2-[(hydroxyacetyl)amino]-4-pyridinyl]methyl] -thio]-N-[4-(trifluoromethoxy)phenyl]-3-pyridinecarboxamide.

5. A parenteral pharmaceutical composition for prophylaxis or treatment of an eye disease which comprises a compound represented by the formula (1):



(1)

wherein

R^1 represents a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, a C_{1-6} alkyl group substituted by one or more halogen atoms, a C_{1-6} alkoxyl group or a C_{1-6} alkoxyl group substituted by one or more halogen atoms; and

R^2 represents a hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkylcarbonyl group or a C_{1-6} alkylcarbonyl group substituted by one or more hydroxyl groups,

or a salt thereof and polyethylene glycol selected from the group consisting of PEG 200, PEG 300, PEG 400 and PEG 600,

wherein the compound represented by the formula (1) or the salt thereof is dissolved in the composition.

6. The parenteral pharmaceutical composition according to claim 5, wherein

R^1 represents a C_{1-6} alkoxyl group or a C_{1-6} alkoxyl group substituted by one or more halogen atoms; and

R^2 represents a C_{1-6} alkylcarbonyl group or a C_{1-6} alkylcarbonyl group substituted by one or more hydroxyl groups in the formula (1).

7. The parenteral pharmaceutical composition according to claim 5, wherein

R^1 represents a C_{1-6} alkoxyl group substituted by one or more halogen atoms;

and

R^2 represents a C_{1-6} alkylcarbonyl group substituted by one or more hydroxyl groups in the formula (1).

8. The parenteral pharmaceutical composition according to claim 5, wherein the compound represented by the formula (1) is 2-[[[2-[(hydroxyacetyl)amino]-4-pyridinyl]methyl] -thio]-N-[4-(trifluoromethoxy)phenyl]-3-pyridinecarboxamide.

~~5. The pharmaceutical composition according to any one of claims 1 to 4, wherein an average molecular weight of the polyethylene glycol is within the range of 100 to 2,000.~~

~~6. The pharmaceutical composition according to any one of claims 1 to 4, wherein an average molecular weight of the polyethylene glycol is within the range of 200 to 600.~~

~~7~~9. The parenteral pharmaceutical composition according to any one of claims 1 to ~~4~~8, wherein the polyethylene glycol is PEG 400.

~~8~~10. The parenteral pharmaceutical composition according to any one of claims 1 to ~~7~~9, wherein the amount of the polyethylene glycol in the pharmaceutical composition is 70 to 99.99% (w/w).

~~9~~11. The parenteral pharmaceutical composition according to any one of claims 1 to ~~8~~10, wherein the amount of the compound represented by the formula (1) or a salt thereof is 0.01 to 20% (w/v).

~~10. The pharmaceutical composition according to any one of claims 1 to 9 for prophylaxis or treatment of an eye disease.~~

~~11~~12. The parenteral pharmaceutical composition according to any one of claims 1 to ~~10~~11, wherein the eye disease is age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, retinal artery occlusion, polypoidal choroidal vasculopathy, retinal angiomatous proliferation, myopic choroidal neovascularization, diabetic macular edema, ocular tumor, radiation retinopathy, iris rubeosis, neovascular glaucoma or proliferative vitreoretinopathy (PVR).

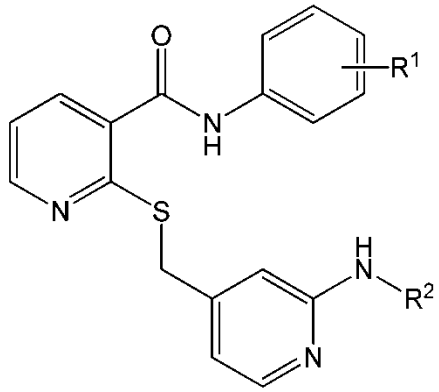
~~12~~13. The parenteral pharmaceutical composition according to any one of claims 1 to

~~10 or 11~~12, which is suitable for intravitreal administration.

~~13~~14. The parenteral pharmaceutical composition according to claim ~~12~~13, which is suitable for being administered 1 to 100 μL per ~~once~~one time.

~~14~~15. The parenteral pharmaceutical composition according to claim ~~12~~13 or ~~13~~14, which is suitable for being administered with an interval of once per week to once per 3 years.

~~15~~16. A method for stabilizing a compound represented by the formula (1):



(1)

wherein

R^1 represents a hydrogen atom, a halogen atom, a hydroxyl group, a $C_{1\text{-}6}$ alkyl group, a $C_{1\text{-}6}$ alkyl group substituted by one or more halogen atoms, a $C_{1\text{-}6}$ alkoxyl group or a $C_{1\text{-}6}$ alkoxyl group substituted by one or more halogen atoms; and

R^2 represents a hydrogen atom, a $C_{1\text{-}6}$ alkyl group, a $C_{1\text{-}6}$ alkylcarbonyl group or a $C_{1\text{-}6}$ alkylcarbonyl group substituted by one or more hydroxyl groups,

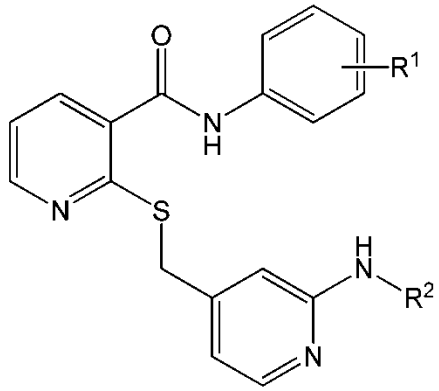
or a salt thereof in a parenteral pharmaceutical composition for prophylaxis or treatment of an eye disease,

which comprises dissolving the compound represented by the formula (1) or a salt thereof in a solvent containing polyethylene glycol.

~~16~~17. The method according to claim ~~15~~16, wherein the compound represented by the formula (1) is 2-[[[2-[(hydroxyacetyl)amino]-4-pyridinyl]methyl]thio]-N-[4-(trifluoromethoxy)phenyl]-3-pyridinecarboxamide.

18. The method according to claim 16 or 17, wherein the polyethylene glycol is PEG 400.

19. Use of a parenteral pharmaceutical composition which comprises a compound represented by the formula (1):



(1)

wherein

R^1 represents a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, a C_{1-6} alkyl group substituted by one or more halogen atoms, a C_{1-6} alkoxyl group or a C_{1-6} alkoxyl group substituted by one or more halogen atoms; and

R^2 represents a hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkylcarbonyl group or a C_{1-6} alkylcarbonyl group substituted by one or more hydroxyl groups,

or a salt thereof and polyethylene glycol whose average molecular weight is within the range of 200 to 600,

wherein the compound represented by the formula (1) or the salt thereof is dissolved in the composition,

in the manufacture of a medicament for prophylaxis or treatment of an eye disease.

20. The use according to claim 19, wherein the compound represented by the formula (1) is 2-[[[2-[(hydroxyacetyl)amino]-4-pyridinyl]methyl] -thio]-N-[4-(trifluoromethoxy)phenyl]-3-pyridinecarboxamide.

21. The use according to claim 19 or 20, wherein the polyethylene glycol is PEG 400.

22. The use according to any one of claims 19 to 21, wherein the amount of the polyethylene glycol in the pharmaceutical composition is 70 to 99.99% (w/w).

23. The use according to any one of claims 19 to 22, wherein the amount of the compound represented by the formula (1) or a salt thereof is 0.01 to 20% (w/v).

24. The use according to any one of claims 19 to 23, wherein the eye disease is age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, retinal artery occlusion, polypoidal choroidal vasculopathy, retinal angiomatous proliferation, myopic choroidal neovascularization, diabetic macular edema, ocular tumor, radiation retinopathy, iris rubeosis, neovascular glaucoma or proliferative vitreoretinopathy (PVR).

25. The use according to any one of claims 19 to 24, wherein the medicament is adapted for intravitreal administration.