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(54) Agent for prophylaxis and treatment of glaucoma

Verbindung zur Vorbeugung und Behandlung von Glaukoma

Agent pour prévenir et traiter le glaucome

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(56) References cited:
EP-A- 0 757 038 **WO-A-98/06433**

- **SAITO TADAMASA ET AL: "Preparation of trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4 - guanidinomethylcyclohexanecarboxamide monomethanesulfonate monohydrate having smooth muscle relaxing activity" HCA, 1996, XP002229795 & JP 08 198876 A (YOSHITOMI PHARMACEUTICAL) 6 August 1996 (1996-08-06)**

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Description

Technical Field

[0001] The present invention relates to a compound and an agent for the prophylaxis and treatment of glaucoma. More specifically, the present invention relates to a compound and an agent for the prophylaxis and treatment of glaucoma, which comprises said compound having a Rho kinase inhibitory activity as an active ingredient.

[0002] Glaucoma is caused by an abnormally high internal pressure of the eyeball, wherein the abnormally high pressure makes the eye grow dim or hurts the eye, which in turn fails the eyesight little by little possibly into blindness. Normally, an aqueous humor continuously circulates in the eyeball and maintains a constant intraocular pressure (10 - 20 mmHg). The pressure is maintained by the circulation of the blood and lymphocytes, elasticity of the eyeball wall, the performance of the control nerves and the like. An abnormality in any of them results in a rise of the intraocular pressure, which may develop glaucoma.

[0003] With the aim of preventing the intraocular pressure from rising or lowering an intraocular pressure that went up, for the prophylaxis and treatment of glaucoma, various drugs have been used. Known eye drops for the therapy of glaucoma include sympathetic agonists such as epinephrine, dipivefrine and the like. Due to mydriatic action, however, these eye drops enhance angle closure when administered to treat narrow angle glaucoma, and may cause not only an acute rise of the intraocular pressure, but also hypertension and pigmentation deposit. In addition, the parasympathetic agonists such as pilocarpine and the like cause side effects such as dark visual field due to miosis and congested eye, iris cyst, posterior synechia, cataract, retinal detachment and the like after a long-term use. Moreover, β-adrenalin blockers such as timolol, pindolol and the like have been widely used, because they lower intraocular pressure by inhibiting the production of aqueous humor without acting on pupils. However, their use is limited, because β-adrenalin blockers have been reported to cause side effects such as local dry feeling of the eye, allergic blepharitis, superficial keratitis and the like, as well as systemic side effects such as bradycardia, heart failure, asthmatic fit and the like. These side effects prevent application of the blockers to patients suffering from such symptoms. A recent suggestion of an aqueous humor outflow promoting effect of α1-adrenalin blockers also suggests potential use of bunazosin hydrochloride and the like as a new therapeutic agent of glaucoma (Ikuo Azuma, Folia Ophthalmol. Jpn.,42,710-714,1991). However, the α1-adrenalin blockers are inevitably associated with conjunctival injection and miosis due to their vasodilating action.

[0004] In the meantime, a compound having a Rho kinase inhibitory activity has been reported to show a hypotensive effect on various hypertension model animals (Masayoshi Uehata, et al., Nature 389, 990-994, 1997). The Rho kinase has been confirmed to be present in corneal epithelial cells (Nirmala SundarRaj. et al., IOVS, 39(7) 1266-1272, 1998). However, it is unknown if Rho kinase is present in other ophthalmic tissues.

[0005] The pharmaceutical use of the compound having a Rho kinase inhibitory activity is disclosed in WO-A-98/06433, and, as a use in the ophthalmic area, is taught to be useful for retinopathy. However, WO-A-98/06433 does not disclose its usefulness against glaucoma or description suggestive of the effect.

[0006] As a compound having a Rho kinase inhibitory activity, a compound of formula (I) to be mentioned later has been reported (WO-A-98/06433). The compound of formula (I) has been already known to be useful as an agent for the prophylaxis and treatment of disorders of circulatory organs such as coronary, cerebral, renal, peripheral artery and the like (e.g., a therapeutic agent of hypertension, a therapeutic agent of angina pectoris, a therapeutic agent of renal and peripheral circulation disorder, a suppressive agent of cerebrovascular contraction and the like), which is potent and long lasting, and also as a therapeutic agent of asthma (JP-A-62-89679, JP-A-3-218356, JP-A-4-273821, JP-A-5-194401, JP-A-6-41080 and WO-A-95/28387).

[0007] JP-A-8-198876 relates to the preparation of trans-N-(1H-pyrazolo[3,4-b]pyridine-4-yl)-4-guanidinomethylcyclohexanecarboxamide monomethane-sulfonate monohydrate which is, *inter alia,* useful for the treatment of glaucoma.

[0008] However, these compounds of the formula (I') are not disclosed to be useful for glaucoma, and there is no description suggestive of such usefulness.

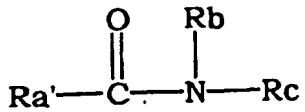
Disclosure of the Invention

[0009] The present invention aims at solving the above-mentioned problems and provides a compound and an agent for the prophylaxis and treatment of glaucoma, which is superior in a prophylactic and therapeutic effect on glaucoma.

[0010] The present inventors have conducted intensive studies and found that a compound having a Rho kinase inhibitory activity also has an intraocular pressure lowering action, an optic disc blood flow improving action and an aqueous outflow promoting action, and that it is useful for the prophylaxis and treatment of various types of glaucoma, which resulted in the completion of the present invention.

[0011] Accordingly, the present invention provides the following.

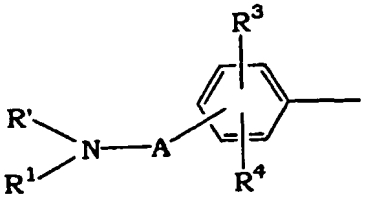
(1) A compound having a Rha kinase activity of the following formula (I')



(I')

wherein

Ra' is a group of the formula



(b')

wherein

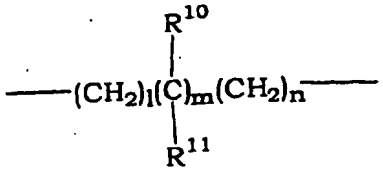
R' is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, or cycloalkyl having 3 to 7 carbon atoms, cycloalkylalkyl wherein the cycloalkyl moiety has 3 to 7 carbon atoms and the alkyl moiety is linear or branched alkyl having 1 to 6 carbon atoms, phenyl or aralkyl wherein the alkyl moiety is alkyl, having 1 to 4 carbon atoms, which optionally has a substituent on the ring,

R^1 is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, or cycloalkyl having 3 to 7 carbon atoms, cycloalkylalkyl wherein the cycloalkyl moiety has 3 to 7 carbon atoms and the alkyl moiety is linear or branched alkyl having 1 to 6 carbon atoms, phenyl or aralkyl wherein the alkyl moiety is alkyl having 1 to 4 carbon atoms, which optionally has a substituent on the ring, or R' and R^1 in combination form, together with the adjacent

R^2 nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom, is hydrogen or linear or branched alkyl having 1 to 10 carbon atoms,

R^3 and R^4 are the same or different and each is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, aralkyl wherein the alkyl moiety is alkyl having 1 to 4 carbon atoms, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or azide, and

A is a group of the formula



(e)

wherein R^{10} and R^{11} are the same or different and each is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, haloalkyl, aralkyl wherein the alkyl moiety is alkyl having 1 to 4 carbon atoms, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl having 3 to 7 carbon atoms in combination and 1, m and n are each 0 or an integer of 1-3,

Rb is a hydrogen, a linear or branched alkyl having 1 to 10 carbon atoms, an aralkyl wherein the alkyl moiety is alkyl having 1 to 4 carbon atoms, an aminoalkyl or a mono- or dialkylaminoalkyl; and

Rc is an optionally substituted hetereocycle containing nitrogen, an optical or cis-trans isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof. for use in the prophylaxis and treatment of glaucoma.

(2) The compound of (1) above, wherein the compound is (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridine-4-yl)-4-(1-aminoethyl)benzamide and/or a pharmaceutically acceptable acid

addition salt thereof.

(3) The compound of (1) or (2) above wherein the compound is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridine-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof.

(4) The compound of (1) to (3) above wherein the pharmaceutically acceptable acid addition salt is a salt, wherein the acid is an inorganic acid selected from hydrochloric acid, hydrobromic acid, and sulfuric acid or an organic acid such as methanesulfonic acid, fumaric acid, maleic acid, mandelic acid, citric acid, tartaric acid, and salicylic acid.

(5) The compound of (1) to (4) above, wherein the acid addition salt is a hydrochloric acid addition salt.

(6) The compound of (1) above for administration to a local site in the eye.

(7) The compound of (6) above for administration in the form of an eye drop.

(8) An agent comprising the compound of anyone of (1) to (7) above for use in the prophylaxis and treatment of glaucoma.

Brief Description of the Drawings

[0012]

Fig. 1 is a graph showing the effect of the eye drop of Example 1 on the normal intraocular pressure, wherein the ordinate shows intraocular pressure, the abscissa shows time after instillation, • shows the eye instilled with the eye drop of Example 1 and ○ shows control eye (n=6, * $p<0.05$, ** $p<0.01$, *** $p<0.001$).
Fig. 2 is a graph showing the effect of the eye drop of Example 1 on the optic disc blood flow kinetic, wherein the ordinate shows relative optic disc blood flow, the abscissa shows time after instillation, ● shows the eye instilled with the eye drop of Example 1 and ○ shows control eye (n=6, * $p<0.05$, ** $p<0.01$, *** $p<0.001$).
Fig. 3 is a graph showing the effect of Compound A on ciliary muscle contraction by carbachol, wherein the ordinate shows contraction rate of ciliary muscle, the abscissa shows concentration of carbachol, ○ shows control, • shows addition of 1×10^{-5} M Compound A, ■ shows addition of 3×10^{-6} M Compound A and ▲ shows addition of 1×10^{-6} M Compound A.
Fig. 4 is a graph showing the effect of the eye drops of Example 2 [0.1% compound A] (a) and Example 5 [0.1% compound C] (b) on the normal intraocular pressure, wherein the ordinate shows intraocular pressure, the abscissa shows time after instillation, ● shows the eye instilled with the eye drop and ○ shows control eye (n=6, * $p<0.05$, ** $p<0.01$ Student's t-test).
Fig. 5 is a graph showing the effect of the eye drops of Example 3 [0.03% compound A] (a) and Example 4 [0.03% compound B] (b) on the normal intraocular pressure, wherein the ordinate shows intraocular pressure, the abscissa shows time after instillation, ● shows the eye instilled with the eye drop and ○ shows control eye (n=6, * $p<0.05$ Student's t-test).
Fig. 6 is a graph showing the effect of the eye drops of Example 6 [0.03% compound C] (c) and Example 7 [0.03% compound D](d) on the normal intraocular pressure, wherein the ordinate shows intraocular pressure, the abscissa shows time after instillation, ● shows the eye instilled with the eye drop and 0 shows control eye (n=6, * $p<0.05$, ** $p<0.01$, *** $p<0.001$ Student's t-test).
Fig. 7 is a graph showing the effect of the eye drops of Example 2 [0.1% compound A] (a) and Example 5 [0.1% compound C] (b) on the optic disc blood flow kinetic, wherein the ordinate shows relative optic disc blood flow, the abscissa shows time after instillation, • shows the eye instilled with the eye drop and ○ shows control eye (n=6, * $p<0.05$, ** $p<0.01$, *** $p<0.001$ paired t-test).

Detailed Description of the Invention

[0013] In the present invention, glaucoma is exemplified by primary open angle glaucoma, normal pressure glaucoma, hypersecretion glaucoma, ocular hypertension, acute angle closure glaucoma, chronic angle closer glaucoma, plateau iris syndrome, combined-mechanism glaucoma, steroid glaucoma, capsular glaucoma, pigmentary glaucoma, secondary glaucoma associated with amyloidosis, neovascular glaucoma, malignant glaucoma.

[0014] In the present invention, Rho kinase means serine/threonine kinase activated along with the activation of Rho. For example, ROKα (ROCKII:Leung, T. et al, J. Biol. Chem., 270, 29051-29054, 1995), p160 ROCK (ROKβ, ROCK-I : Ishizaki, T. et al, The EMBO J., 15(8), 1885-1893, 1996) and other proteins having a serine/threonine kinase activity

are exemplified.

[0015] The compounds having a Rho kinase inhibitory activity used as the active ingredient in the present invention are the compounds of the formula (I'). In the present invention, a compound having one kind of Rho kinase inhibitory activity can be used alone or, where necessary, several kinds of the compounds can be used.

[0016] In the present specification, each symbol of the formula (I') is defined as follows.

[0017] Alkyl at R' and R^1 is linear or branched alkyl having 1 to 10 carbon atoms, which is exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl , with preference given to alkyl having 1 to 4 carbon atoms.

[0018] Cycloalkyl at R' and R^1 has 3 to 7 carbon atoms and is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl .

[0019] Cycloalkylalkyl at R' and R^1 is that wherein the cycloalkyl moiety is the above-mentioned cycloalkyl having 3 to 7 carbon atoms and the alkyl moiety is linear or branched alkyl having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl and the like), which is exemplified by cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclopropylethyl, cyclopentylethyl, cyclohexylethyl, cycloheptylethyl, cyclopropylpropyl, cyclopentylpropyl, cyclohexylpropyl, cycloheptylpropyl, cyclopropylbutyl, cyclopentylbutyl, cyclohexylbutyl, cycloheptylbutyl, cyclopropylhexyl, cyclopentylhexyl, cyclohexylhexyl, cycloheptylhexyl .

[0020] Aralkyl at R' and R^1 is that wherein alkyl moiety is alkyl having 1 to 4 carbon atoms and is exemplified by phenylalkyl such as benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl and the like.

[0021] The substituent of optionally substituted cycloalkyl, cycloalkylalkyl, phenyl and aralkyl on the ring at R' and R^1 is halogen (e.g., chlorine, bromine, fluorine and iodine), alkyl (same as alkyl at R' and R^1), alkoxy (linear or branched alkoxy having 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, hexyloxy), aralkyl (same as aralkyl at R' and R^1) or haloalkyl (alkyl at , R' and R^1 which is substituted by 1-5 halogen, and exemplified by fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl and the like), nitro, amino, cyano, azide.

[0022] The group formed by R' and R^1 in combination together with the adjacent nitrogen atom, which forms a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom is preferably a 5 or 6-membered ring and bonded ring thereof. Examples thereof include 1-pyrrolidinyl, piperidino, 1-piperazinyl, morpholino, thiomorpholino, 1-imidazolyl, 2,3-dihydrothiazol-3-yl . The substituent of the optionally substituted nitrogen atom is exemplified by alkyl, aralkyl, haloalkyl . As used herein, alkyl, aralkyl and haloalkyl are as defined for R' and R^1.

[0023] Alkyl at R^2 is as defined for R' and R^1.

[0024] Halogen, alkyl, alkoxy and aralkyl at R^3 and R^4 are as defined for R' and R^1.

[0025] Acyl at R^3 and R^4 is alkanoyl having 2 to 6 carbon atoms (e.g., acetyl, propionyl, butyryl, valeryl, pivaloyl), benzoyl or phenylalkanoyl wherein the alkanoyl moiety has 2 to 4 carbon atoms (e.g., phenylacetyl, phenylpropionyl, phenylbutyryl).

[0026] Alkylamino at R^3 and R^4 is that wherein the alkyl moiety is alkylamino having linear or branched alkyl having 1 to 6 carbon atoms. Examples thereof include methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, sec-butylamino, tert-butylamino, pentylamino, hexylamino.

[0027] Acylamino at R^3 and R^4 is that wherein acyl moiety is alkanoyl having 2 to 6 carbon atoms, benzyl or the alkanoyl moiety is phenylalkanoyl having 2 to 4 carbon atoms, which is exemplified by acetylamino, propionylamino, butyrylamino, valerylamino, pivaloylamino, benzoylamino, phenylacetylamino, phenylpropionylamino, phenylbutyrylamino.

[0028] Alkylthio at R^3 and R^4 is that wherein the alkyl moiety is linear or branched alkyl having 1 to 6 carbon atoms, which is exemplified by methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, hexylthio .

[0029] Aralkyloxy at R^3 and R^4 is that wherein the alkyl moiety is alkyl having 1 to 4 carbon atoms, which is exemplified by benzyloxy, 1-phenylethyloxy, 2-phenylethyloxy, 3-phenylpropyloxy, 4-phenylbutyloxy.

[0030] Aralkylthio at R^3 and R^4 is that wherein the alkyl moiety is alkyl having 1 to 4 carbon atoms, which is exemplified by benzylthio,1-phenylethylthio,2-phenylethylthio,3-phenylpropylthio,4-phenylbutylthio.

[0031] Alkoxycarbonyl at R^3 and R^4 is that wherein the alkoxy moiety is linear or branched alkoxy having 1 to 6 carbon atoms, which is exemplified by methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl.

[0032] Alkylcarbamoyl at R^3 and R^4 is carbamoyl mono- or di-substituted by alkyl having 1 to 4 carbon atoms, which is exemplified by methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, propylcarbamoyl, dipropylcarbamoyl, butylcarbamoyl, dibutylcarbamoyl.

[0033] Hydroxyalkyl at R^{10} and R^{11} is linear or branched alkyl having 1 to 6 carbon atoms which is substituted by 1 to 3 hydroxy, which is exemplified by hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl . Alkyl at R^{10} and R^{11} is as defined for R' and R^1; haloalkyl and alkoxycarbonyl at R^{10} and R^{11} are as defined for R' and R^1; aralkyl at R^{10} and R^{11} is as defined for R' and R^1; and cycloalkyl formed by R^{10} and R^{11} in combination is the same

as cycloalkyl at R' and R^1.

[0034] Alkyl at Rb is as defined for R' and R^1.

[0035] Aralkyl at Rb is as defined for R' and R^1.

[0036] Aminoalkyl at Rb is a linear or branched alkyl having 1 to 6 carbon atoms, which is substituted by amino, which is exemplified by aminomethyl, 2-aminoethyl, 1-aminoethyl, 3-aminopropyl, 4-aminobutyl, 5-aminopentyl, and 6-aminohexyl.

[0037] Mono- or dialkylaminoalkyl at Rb is mono- or di-substituted aminoalkyl with alkyl having 1 to 4 carbon atoms, which is exemplified by methylaminomethyl, dimethylaminomethyl, ethylaminomethyl, diethylaminomethyl, propylaminomethyl, dipropylaminomethyl, butylaminomethyl, dibutylaminomethyl, 2-dimethylaminoethyl, and 2-diethylaminoethyl.

[0038] The heterocycle when single ring containing nitrogen at Rc is pyridine, pyrimidine, pyridazine, triazine, pyrazole, triazole , and when it is a condensed ring, it is exemplified by pyrrolopyridine (e.g., 1H-pyrrolo[2,3-b]pyridine, 1H-pyrrolo [3,2-b]pyridine, 1H-pyrrolo[3,4-b]pyridine), pyrazolopyridine (e.g., 1H-pyrazolo[3,4-b]pyridine, 1H-pyrazolo[4,3-b]pyridine), imidazopyridine (e.g., 1H-imidazo[4,5-b]pyridine), pyrrolopyrimidine (e.g., 1H-pyrrolo[2,3-d]pyrimidine, 1H-pyrrolo [3,2-d]pyrimidine, 1H-pyrrolo[3,4-d]pyrimidine), pyrazolopyrimidine (e.g., 1H-pyrazolo[3,4-d]pyrimidine, pyrazolo[1,5-a] pyrimidine, 1H-pyrazolo[4,3-d]pyrimidine), imidazopyrimidine (e.g., imidazo[1,2-a]pyrimidine, 1H-imidazo[4,5-d] pyrimidine), pyrrolotriazine (e.g., pyrrolo[1,2-a]-1,3,5-triazine, pyrrolo[2,1-f]-1,2,4-triazine), pyrazolotriazine (e.g., pyrazolo[1,5-a]-1,3,5-triazine), triazolopyridine (e.g., 1H-1,2,3-triazolo[4,5-b]pyridine), triazolopyrimidine (e.g., 1,2,4-triazolo[1,5-a]pyrimidine, 1,2,4-triazolo[4,3-a]pyrimidine, 1H-1,2,3-triazolo[4,5-d]pyrimidine), cinnoline, quinazoline, quinoline, pyridopyridazine (e.g., pyrido[2,3-c]pyridazine), pyridopyrazine (e.g., pyrido[2,3-b]pyrazine), pyridopyrimidine (e.g., pyrido[2,3-d]pyrimidine, pyrido(3,2-d]pyrimidine), pyrimidopyrimidine (e.g., pyrimido[4,5-d]pyrimidine, pyrimido [5,4-d]pyrimidine), pyrazinopyrimidine (e.g., pyrazino[2,3-d]pyrimidine), naphthyridine (e.g., 1,8-naphthyridine), tetrazolopyrimidine (e.g., tetrazolo[1,5-a]pyrimidine), thienopyridine (e.g., thieno[2,3-b]pyridine), thienopyrimidine (e.g., thieno[2,3-d]pyrimidine), thiazolopyridine (e.g., thiazolo[4,5-b]pyridine, thiazolo[5,4-b]pyridine), thiazolopyrimidine (e.g., thiazolo[4,5-d]pyrimidine, thiazolo[5,4-d]pyrimidine), oxazolopyridine (e.g., oxazolo[4,5-b]pyridine, oxazolo[5,4-b]pyridine), oxazolopyrimidine (e.g., oxazolo[4,5-d]pyrimidine, oxazolo[5,4-d]pyrimidine), furopyridine (e.g., furo[2,3-b]pyridine, furo[3,2-b]pyridine), furopyrimidine (e.g., furo[2,3-d]pyrimidine, furo[3,2-d]pyrimidine), 2,3-dihydropyrrolopyridine(e.g., 2,3-dihydro-1H-pyrrolo[2,3-b]pyridine, 2,3-dihydro-1H-pyrrolo[3,2-b]pyridine), 2,3-dihydropyrrolopyrimidine (e.g., 2,3-dihydro-1H-pyrrolo[2,3-d]pyrimidine, 2,3-dihydro-1H-pyrrolo[3,2-d]pyrimidine), 5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine, 5,6,7,8-tetrahydro-1,8-naphthyridine, 5,6,7,8-tetrahydroquinoline . When these rings form a hydrogenated aromatic ring, the carbon atom in the ring may be carbonyl and includes, for example, 2,3-dihydro-2-oxopyrrolopyridine, 2,3-dihydro-2,3-dioxopyrrolopyridine, 7,8-dihydro-7-oxo-1,8-naphthyridine, 5,6,7,8-tetrahydro-7-oxo-1,8-naphthyridine , with preference given to pyridin and pyrrolopyridine.

[0039] These rings may be substituted by a substituent such as halogen, alkyl, alkoxy, aralkyl, haloalkyl, nitro, amino, alkylamino, cyano, formyl, acyl, aminoalkyl, mono- or dialkylaminoalkyl, azide, carboxy, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, alkoxyalkyl (e.g., methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl), optionally substituted hydrazino .

[0040] As used herein, the substituent of the optionally substituted hydrazino includes alkyl, aralkyl, nitro, cyano , wherein alkyl and aralkyl are as defined for R' and R^1 and exemplified by methylhydrazino, ethylhydrazino, benzylhydrazino .

[0041] The compound of the formula (I') is exemplified by contain of the following compounds.

compounds which do not fall which the general formula of claim 1 do not form part of the present invention. (1) 4-(2-pyridylcarbamoyl)piperidine
(2) 1-benzyloxycarbonyl-4-(4-pyridylcarbamoyl)piperidine
(3) 1-benzoyl-4-(4-pyridylcarbamoyl)piperidine
(4) 1-propyl-4-(4-pyridylcarbamoyl)piperidine
(5) [3-(2-(2-thienylmethyl)phenoxy)-2-hydroxypropyl]-4-(4-pyridylcarbamoyl)piperidine
(6) 4-(4-pyridylcarbamoyl)piperidine
(7) 1-benzyl-4-(4-pyridylcarbamoyl)-1,2,5,6-tetrahydropyridine
(8) 3-(4-pyridylcarbamoyl)piperidine
(9) 1-benzyl-3-(4-pyridylcarbamoyl)piperidine
(10) 1-(2-(4-benzyloxyphenoxy)ethyl)-4-(N-(2-pyridyl)-N-benzylcarbamoyl)pyridine
(11) 1-formyl-4-(4-pyridylcarbamoyl)piperidine
(12) 4-(3-pyridylcarbamoyl)piperidine
(13) 1-isopropyl-4-(4-pyridylcarbamoyl)piperidine
(14) 1-methyl-4-(4-pyridylcarbamoyl)piperidine
(15) 1-hexyl-4-(4-pyridylcarbamoyl)piperidine
(16) 1-benzyl-4-(4-pyridylcarbamoyl)piperidine

(17) 1-(2-phenylethyl)-4-(4-pyridylcarbamoyl)piperidine
(18) 1-(2-(4-methoxyphenyl)ethyl)-4-(4-pyridylcarbamoyl)piperidine
(19) 1-(2-(4-methoxyphenyl)ethyl)-4-(2-pyridylcarbamoyl)piperidine
(20) 1-(2-(4-chlorophenyl)ethyl)-4-(4-pyridylcarbamoyl)piperidine
(21) 1-diphenylmethyl-4-(2-pyridylcarbamoyl)piperidine
(22) 1-[2-(4-(5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl)phenyl)ethyl]-4-(2-pyridylcarbamoyl)piperidine
(23) 1-(4-(4,5-dihydro-2-furyl)phenyl)-4-(4-pyridylcarbamoyl)-piperidine
(24) 1-(2-nitrophenyl)-4-(4-pyridylcarbamoyl)piperidine
(25) 1-(2-aminophenyl)-4-(4-pyridylcarbamoyl)piperidine
(26) 1-nicotinoyl-4-(4-pyridylcarbamoyl)piperidine
(27) 1-isonicotinoyl-4-(4-pyridylcarbamoyl)piperidine
(28) 1-(3,4,5-trimethoxybenzoyl)-4-(4-pyridylcarbamoyl)piperidine
(29) 1-acetyl-4-(4-pyridylcarbamoyl)piperidine
(30) 1-(3-(4-fluorobenzoyl)propyl)-4-(4-pyridylcarbamoyl)-piperidine
(31) 1-(3-(4-fluorobenzoyl)propyl)-4-(2-pyridylcarbamoyl)-piperidine
(32) 1-(1-(4-hydroxybenzoyl)ethyl)-4-(2-pyridylcarbamoyl)-piperidine
(33) 1-(1-(4-benzyloxybenzoyl)ethyl)-4-(2-pyridylcarbamoyl)-piperidine
(34) 1-(2-(4-hydroxyphenoxy)ethyl)-4-(2-pyridylcarbamoyl)-piperidine
(35) 1-(4-(4-fluorophenyl)-4-hydroxybutyl)-4-(4-pyridylcarbamoyl)piperidine
(36) 1-(1-methyl-2-(4-hydroxyphenyl)-2-hydroxyethyl)-4-(2-pyridylcarbamoyl)piperidine
(37) 1-cinnamyl-4-(2-pyridylcarbamoyl)piperidine
(38) 1-(2-hydroxy-3-phenoxypropyl)-4-(4-pyridylcarbamoyl)-piperidine
(39) 1-(2-hydroxy-3-phenoxypropyl)-4-(3-pyridylcarbamoyl)-piperidine
(40) 1-(2-hydroxy-3-phenoxypropyl)-4-(2-pyridylcarbamoyl)-piperidine
(41) 1-(2-phenylethyl)-4-[N-(2-pyridyl)-N-(2-(N,N-dimethylamino)ethyl)carbamoyl]piperidine
(42) 1-benzyloxycarbonyl-4-(2-pyridylcarbamoyl)piperidine
(43) 1-(3-chlorophenyl)carbamoyl-4-(4-pyridylcarbamoyl)piperidine
(44) 1-[N-(2-pyridyl)-N-(2-(N,N-dimethylamino)ethyl)-carbamoyl]piperidine
(45) 1-methyl-4-(4-pyridylcarbamoyl)-1,2,5,6-tetrahydropyridine
(46) 1-nicotinoyl-3-(4-pyridylcarbamoyl)piperidine
(47) 1-[2-(4-fluorobenzoyl)ethyl]-4-(4-pyridylcarbamoyl)piperidine
(48) 1-(6-chloro-2-methylimidazo[1,2-a]pyridine-3-carbonyl)-4-(4-pyridylcarbamoyl)piperidine
(49) 1-(4-nitrobenzyl)-4-(4-pyridylcarbamoyl)piperidine
(50) 1-hexyl-4-(4-pyridylcarbamoyl)piperidine
(51) 1-benzyloxycarbonyl-4-(2-chloro-4-pyridylcarbamoyl)piperidine
(52) 4-(2-chloro-4-pyridylcarbamoyl)piperidine
(53) 1-(2-chloronicotinoyl)-4-(4-pyridylcarbamoyl)piperidine
(54) 3-(2-chloro-4-pyridylcarbamoyl)piperidine
(55) 1-(4-phthalimidobutyl)-4-(4-pyridylcarbamoyl)piperidine
(56) 1-(3,5-di-tert-butyl-4-hydroxycinnamoyl)-4-(4-pyridylcarbamoyl)piperidine
(57) 1-carbamoylmethyl-4-(4-pyridylcarbamoyl)piperidine
(58) 1-benzyloxycarbonyl-4-(5-nitro-2-pyridylcarbamoyl)piperidine
(59) 4-(5-nitro-2-pyridylcarbamoyl)piperidine
(60) trans-4-benzyloxycarboxamidomethyl-1-(4-pyridylcarbamoyl)-cyclohexane
(61) trans-4-aminomethyl-1-(4-pyridylcarbamoyl)cyclohexane
(62) trans-4-formamidomethyl-1-(4-pyridylcarbamoyl)cyclohexane
(63) trans-4-dimethylaminomethyl-1-(4-pyridylcarbamoyl)cyclohexane
(64) N-benzylidene-trans-(4-pyridylcarbamoyl)cyclohexylmethylamine
(65) trans-4-benzylaminomethyl-1-(4-pyridylcarbamoyl)cyclohexane
(66) trans-4-isopropylaminomethyl-1-(4-pyridylcarbamoyl)-cyclohexane
(67) trans-4-nicotinoylaminomethyl-1-(4-pyridylcarbamoyl)-cyclohexane
(68) trans-4-cyclohexylaminomethyl-1-(4-pyridylcarbamoyl)-cyclohexane
(69) trans-4-benzyloxycarboxamide-1-(4-pyridylcarbamoyl)-cyclohexane
(70) trans-4-amino-1-(4-pyridylcarbamoyl)cyclohexane
(71) trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(72) trans-4-aminomethyl-cis-2-methyl-1-(4-pyridylcarbamoyl)-cyclohexane
(73) (+)-trans-4-(1-benzyloxycarboxamidopropyl)-1-cyclohexanecarboxylic acid
(74) (+)-trans-4-(1-benzyloxycarboxamidopropyl)-1-(4-pyridylcarbamoyl)cyclohexane

(75) (-)-trans-4-(1-benzyloxycarboxamidpropyl)-1-(4-pyridylcarbamoyl)cyclohexane
(76) (+)-trans-4-(1-aminopropyl)-1-(4-pyridylcarbamoyl)cyclohexane
(77) (-)-trans-4-(1-aminopropyl)-1-(4-pyridylcarbamoyl)cyclohexane
(78) (-)-trans-4-(1-benzyloxycarboxamidoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(79) (+)-trans-4-(1-benzyloxycarboxamidoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(80) (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(81) (-)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(82) trans-4-(4-chlorobenzoyl)aminomethyl-1-(4-pyridylcarbamoyl)cyclohexane
(83) trans-4-aminomethyl-1-(2-pyridylcarbamoyl)cyclohexane
(84) trans-4-benzyloxycarboxamidomethyl-1-(2-pyridylcarbamoyl)-cyclohexane
(85) trans-4-methylaminomethyl-1-(4-pyridylcarbamoyl)cyclohexane
(86) trans-4-(N-benzyl-N-methylamino)methyl-1-(4-pyridylcarbamoyl)cyclohexane
(87) trans-4-aminomethyl-1-(3-pyridylcarbamoyl)cyclohexane
(88) trans-4-aminomethyl-1-[(3-hydroxy-2-pyridyl)carbamoyl]-cyclohexane
(89) trans-4-benzyloxycarboxamidomethyl-1-(3-pyridylcarbamoyl)-cyclohexane
(90) trans-4-benzyloxycarboxamidomethyl-1-[(3-benzyloxy-2-pyridyl)carbamoyl]cyclohexane
(91) trans-4-phthalimidomethyl-1-(4-pyridylcarbamoyl)cyclohexane
(92) trans-4-benzyloxycarboxamidomethyl-1-(3-methyl-4-pyridylcarbamoyl)cyclohexane
(93) trans-4-aminomethyl-1-(3-methyl-4-pyridylcarbamoyl)-cyclohexane
(94) 4-(trans-4-benzyloxycarboxamidomethylcyclohexylcarbonyl)amino-2,6-dimethylpyridine-N-oxide
(95) 4-(trans-4-aminomethylcyclohexylcarbonyl)amino-2,6-dimethylpyridine-N-oxide
(96) trans-4-aminomethyl-1-(2-methyl-4-pyridylcarbamoyl)-cyclohexane
(97) trans-4-(1-benzyloxycarboxamidoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(98) trans-4-(1-amino-1-methylethyl)-1-(4-pyridylcarbamoyl)-cyclohexane
(99) trans-4-(2-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(100) trans-4-(2-amino-1-methylethyl)-1-(4-pyridylcarbamoyl)-cyclohexane
(101) trans-4-(1-aminopropyl)-1-(4-pyridylcarbamoyl)cyclohexane
(102) trans-4-aminomethyl-trans-1-methyl-1-(4-pyridylcarbamoyl)-cyclohexane
(103) trans-4-benzylaminomethyl-cis-2-methyl-1-(4-pyridylcarbamoyl)cyclohexane
(104) trans-4-(1-benzyloxycarboxamide-1-methylethyl)-1-(4-pyridylcarbamoyl)cyclohexane
(105) trans-4-benzyloxycarboxamidomethyl-1-(N-methyl-4-pyridylcarbamoyl)cyclohexane
(106) trans-4-(1-acetamide-1-methylethyl)-1-(4-pyridylcarbamoyl)-cyclohexane
(107) trans-N-(6-amino-4-pyrimidyl)-4-aminomethylcyclohexanecarboxamide
(108) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
(109) (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide '
(110) trans-N-(IH-pyrrolo[2,3-b]pyridin-4-yl)-4-(I-amino-I-methylethyl)cyclohexanecarboxamide
(111) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
(112) (+)-trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
(113) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-amino-1-methylethyl)cyclohexanecarboxamide
(114) (+)-trans-N-(2-amino-4-pyridyl)-4-(1-aminoethyl)-cyclohexanecarboxamide
(115) trans-N-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-aminomethylcyclohexanecarboxamide
(116) (+)-trans-N-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
(117) trans-N-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(1-amino-1 methylethyl)cyclohexanecarboxamide
(118) trans-N-(4-pyrimidinyl)-4-aminomethylcyclohexanecarboxamide
(119) trans-N-(3-amino-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
(120) trans-N-(7H-imidazo[4,5-d]pyrimidin-6-yl)-4-aminomethylcyclohexanecarboxamide
(121) trans-N-(3H-1,2,3-triazolo[4,5-d]pyrimidin-7-yl)-4-aminomethylcyclohexanecarboxamide
(122) trans-N-(1-benzyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
(123) trans-N-(1H-5-pyrazolyl)-4-aminomethylcyclohexanecarboxamide
(124) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
(125) trans-N-(4-pyridazinyl)-4-aminomethylcyclohexanecarboxamide
(126) trans-N-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-aminomethylcyclohexanecarboxamide
(127) trans-N-(2-amino-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
(128) trans-N-(thieno[2,3-d]pyrimidin-4-yl)-4-aminomethylcyclohexanecarboxamide
(129) trans-N-(5-methyl-1,2,4-triazolo[1,5-a]pyrimidin-7-yl)-4-aminomethylcyclohexanecarboxamide
(130) trans-N-(3-cyano-5-methylpyrazolo[1,5-a]pyrimidin-7-yl)-4-aminomethylcyclohexanecarboxamide
(131) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-amino-1-methylethyl)cyclohexanecarboxamide
(132) trans-N-(2-(1-pyrrolidinyl)-4-pyridyl)-4-aminomethylcyclohexanecarboxamide

(133) trans-N-(2,6-diamino-4-pyrimidyl)-4-aminomethylcyclohexanecarboxamide
(134) (+)-trans-N-(7-methyl-1,8-naphthyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
(135) trans-N-(1-benzyloxymethylpyrrolo[2,3-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
(136) (+)-trans-N-(1-methylpyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
(137) trans-N-benzyl-N-(2-benzylamino-4-pyridyl)-4-(1-amino-1-methylethyl)cyclohexanecarboxamide
(138) trans-N-(2-azide-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
(139) trans-N-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-aminomethylcyclohexanecarboxamide
(140) trans-N-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-amino-1-methylethyl)cyclohexanecarboxamide
(141-1) trans-N-(2-carboxy-4-pyridyl)-4-aminomethylcyclohexanecarboxamide
(141-2) (R)-(+)-trans-N-(3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
(142) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-guanidinomethylcyclohexanecarboxamide
(143) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-guanidinomethylcyclohexanecarboxamide
(144) trans-N-(4-pyridyl)-4-guanidinomethylcyclohexanecarboxamide
(145) trans-N-(1-methylpyrrolo[2,3-b]pyridin-4-yl)-4-(guanidinomethyl)cyclohexanecarboxamide
(146) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(2-imidazolin-2-yl)aminomethylcyclohexanecarboxamide
(147) trans-N-(1-benzyloxymethylpyrrolo[2,3-b]pyridin-4-yl)-4-guanidinomethylcyclohexanecarboxamide
(148) trans-N-(2-amino-4-pyridyl)-4-guanidinomethylcyclohexanecarboxamide
(149) trans-N-(1-benzyloxymethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(2-imidazolin-2-yl)aminomethylcyclohexanecarboxamide
(150) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3-benzylguanidinomethyl)-cyclohexanecarboxamide
(151) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3-phenylguanidinomethyl)-cyclohexanecarboxamide
(152) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3-propylguanidinomethyl)-cyclohexanecarboxamide
(153) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(3-octylguanidinomethyl)-cyclohexanecarboxamide
(154) trans-N-(1-benzyloxymethylpyrrolo[2,3-b]pyridin-4-yl)-4-(2-benzyl-3-ethylguanidinomethyl)cyclohexanecarboxamide
(155) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(imidazol-2-yl)aminomethylcyclohexanecarboxamide
(156) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(thiazol-2-yl)aminomethylcyclohexanecarboxamide
(157) (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide
(158) N-(4-pyridyl)-4-(1-amino-1-methylethyl)benzamide
(159) N-(4-pyridyl)-4-aminomethyl-2-benzyloxybenzamide
(160) N-(4-pyridyl)-4-aminomethyl-2-ethoxybenzamide
(161) (R)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)-3-nitrobenzamide
(162) (R)-(-)-N-(4-pyridyl)-3-amino-4-(1-aminoethyl)benzamide
(163) (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)-3-chlorobenzamide
(164) N-(4-pyridyl)-3-aminomethylbenzamide
(165) (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide
(166) (R)-(+)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide
(167) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-guanidinomethylbenzamide
(168) N-(4-pyridyl)-4-guanidinomethylbenzamide
(169) (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)-3-fluorobenzamide
(170) N-(4-pyridyl)-4-aminomethylbenzamide
(171) N-(4-pyridyl)-4-aminomethyl-2-hydroxybenzamide
(172) N-(4-pyridyl)-4-(2-aminoethyl)benzamide
(173) N-(4-pyridyl)-4-aminomethyl-3-nitrobenzamide
(174) N-(4-pyridyl)-3-amino-4-aminomethylbenzamide
(175) (S)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide
(176) (S)-(-)-N-(4-pyridyl)-2-(1-aminoethyl)benzamide
(177) (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)-2-chlorobenzamide
(178) (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-(3-propylguanidino)ethyl)benzamide
(179) (R)-(-)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)-3-azidebenzamide
(180) (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)-2-nitrobenzamide
(181) (R)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)-3-ethoxybenzamide
(182) (R)-(+)-N-(3-iodo-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide
(183) (R)-(+)-N-(3-iodo-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)-3-azidebenzamide
(184) (R)-(-)-N-(4-pyridyl)-4-(1-aminoethyl)-3-hydroxybenzamide
(185) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-guanidinomethyl-3-nitrobenzamide
(186) (R)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-guanidinoethyl)-3-nitrobenzamide
(187) (R)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-aminoethyl)-2-nitrobenzamide

(188) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-guanidinobenzamide
(189) (R)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-aminoethyl)-3-nitrobenzamide
(190) (R)-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-guanidinoethyl)benzamide
(191) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-(1-amino-2-hydroxyethyl)benzamide
(192) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-aminomethyl-3-nitrobenzamide
(193) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-piperidinecarboxamide
(194) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-piperidinecarboxamide
(195) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1-aminoacetyl-4-piperidinecarboxamide
(196) N-(1-methoxymethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-4-piperidinecarboxamide
(197) N-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)-4-piperidinecarboxamide
(198) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-(2-phenylethyl)-4-piperidinecarboxamide
(199) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-amidino-4-piperidinecarboxamide
(200) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-(3-phenylpropyl)-4-piperidinecarboxamide
(201) N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-benzyl-4-piperidinecarboxamide
(202) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1-(2-phenylethyl)-4-piperidinecarboxamide
(203) N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1-(3-phenylpropyl)-4-piperidinecarboxamide

[0042] Preferred are compounds (80), (109), (110), (112), (115), (142), (143), (144), (145), (153), (157), (163), (165), (166) and (179).

[0043] The compound of formula (I') having a Rho kinase inhibitory activity may be a pharmaceutically acceptable acid addition salt, wherein the acid is exemplified by inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid , and organic acid such as methanesulfonic acid, fumaric acid, maleic acid, mandelic acid, citric acid, tartaric acid, salicylic acid . A compound having a carboxylic group can be converted to a salt with a metal such as sodium, potassium, calcium, magnesium, aluminum and the like, a salt with an amino acid such as lysine . Further, monohydrate, dihydrate, 1/2 hydrate, 1/3 hydrate, 1/4 hydrate, 2/3 hydrate, 3/2 hydrate, 6/5 hydrate are encompassed in the present invention.

[0044] The compound of the formula (I) can be synthesized by a method described in, for example, JP-A-62-89679, JP-A-3-218356, JP-A-5-194401, JP-A-6-41080, WO-A-95/28387, WO-A-98/06433 .

[0045] When the above-mentioned compound having a Rho kinase inhibitory activity has an optical isomer, its racemate or cis-trans isomers, all of them can be used in the present invention. These isomers can be isolated by a conventional method or can be produced using starting materials of the isomers.

[0046] A compound having a Rho kinase inhibitory activity, of the formula (I'), an isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof have intraocular pressure lowering action, optic disc blood flow improving action and aqueous outflow promoting action in mammals inclusive of human, cow, horse, dog, mouse, rat . Therefore, they can be used as an agent for the prophylaxis and treatment of various types of glaucoma, such as primary open angle glaucoma, normal pressure glaucoma, hypersecretion glaucoma, ocular hypertension, acute angle closure glaucoma, chronic angle closer glaucoma, plateau iris syndrome, combined-mechanism glaucoma, steroid glaucoma, capsular glaucoma, pigmentary glaucoma, secondary glaucoma associated with amyloidosis, neovascular glaucoma, malignant glaucoma .

[0047] The agent for the prophylaxis and treatment of glaucoma of the present invention is administered orally or parenterally. The dosage form may be, for example, oral preparation such as tablet, capsule, syrup , or parenteral preparation such as liquid injection (e.g., solution, emulsion, suspension), external agent [e.g., ointment (particularly eye ointment), eye drop], . In consideration of the influence and effect on other circulatory systems, the dosage form of administration to local site in the eye is preferable. The dosage form of eye drop or eye ointment is particularly preferable.

[0048] A preparation having the aforementioned dosage form can be prepared by mixing the inventive compound with an additive necessary for formulating a preparation, such as typical carrier, excipient, binder, stabilizer and by following a conventional method. For example, the compound of formula (I') having a Rho kinase inhibitory activity is mixed with a pharmaceutically acceptable carrier (e.g., excipient, binder, disintegrator, corrective, corrigent, emulsifier, diluent, solubilizer) to give a pharmaceutical composition or a pharmaceutical preparation in the form of tablet, pill, powder, granule, capsule, troche, syrup, liquid, emulsion, suspension, injection (e.g., liquid, suspension), suppository, inhalant, percutaneous absorber, eye drop, eye ointment in the form suitable for oral or parenteral preparation.

[0049] When preparing a solid preparation, additives such as sucrose, lactose, cellulose sugar, D-mannitol, maltitol, dextran, starches, agar, arginates, chitins, chitosans, pectines, tragacanth gum, gum arabic, gelatins, collagens, casein, albumin, calcium phosphate, sorbitol, glycine, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, glycerol, polyethyleneglycol, sodium hydrogencarbonate, magnesium stearate, talc are used. Tablets can be applied with a typical coating, where necessary, to give sugar coated tablets, enteric tablets, film-coated tablets, two-layer tablets and multi-layer tablets.

[0050] When preparing a semi-solid preparation, animal and plant fats and oils (e.g., olive oil, corn oil, castor oil), mineral fats and oils (e.g., petrolatum, white petrolatum, solid paraffin), wax (e.g., jojoba oil, carnauba wax, bee wax),

partly or entirely synthesized glycerol fatty acid esters (e.g., lauric acid, myristic acid, palmitic acid), are used. Examples of commercially available products of these include Witepsol (manufactured by Dynamitnovel Ltd.), Farmazol (NOF Corporation) .

[0051] When preparing a liquid preparation, an additive, such as sodium chloride, glucose, sorbitol, glycerol, olive oil, propylene glycol, ethyl alcohol , is used.

[0052] The liquid preparation may be, for example, injection, eye drop .

[0053] When preparing an injection, a sterile aqueous solution such as physiological saline, isotonic solution, oil (e.g., sesame oil and soybean oil) are used. Where necessary, a suitable suspending agent such as sodium carboxymethylcellulose, nonionic surfactant, solubilizer (e.g., benzyl benzoate and benzyl alcohol), can be concurrently used.

[0054] Moreover, when an eye drop is prepared, an aqueous liquid or solution is used, which is particularly a sterile injectable aqueous solution. The eye drop can appropriately contain various additives such as buffer, stabilizer, wetting agent, emulsifier, suspending agent, surfactant, isotonicity agent, preservative and thickener.

[0055] The buffer may be, for example, phosphate buffer, borate buffer, citrate buffer, tartrate buffer, acetate buffer, amino acid

[0056] The stabilizer may be, for example, sodium edetate, citric acid .

[0057] The wetting agent may be, for example, glycerol .

[0058] The emulsifier may be, for example, polyvinylpyrrolidone .

[0059] The suspending agent may be, for example, hydroxypropylmethylcellulose, methylcellulose .

[0060] The surfactant may be, for example, polysorbate 80, polyoxyethylene hydrogenated castor oil .

[0061] The isotonicity agent may be, for example, saccharides such as sorbitol, glucose, mannitol , polyhydric alcohols such as glycerol, propylene glycol , salts such as sodium chloride .

[0062] The preservative may be, for example, quaternary ammonium salt such as benzalkonium chloride, benzethonium chloride , p-hydroxybenzoate such as methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate , benzyl alcohol, phenethyl alcohol, sorbic acid and salts thereof, thimerosal, chlorobutanol .

[0063] The thickener may be, for example, hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, salts thereof .

[0064] When in use as an eye drop, pH is preferably adjusted generally to 4 - 9, preferably 6 - 8.5.

[0065] When the preparation is an eye ointment, an ointment base (e.g., petrolatum, lanolin, plastibase and the like), a preservative (e.g., benzalkonium chloride, p-hydroxybenzoate, chlorobutanol), are appropriately selected and used for production.

[0066] The agent for the prophylaxis and treatment of glaucoma of the present invention contains an active ingredient in a proportion of 0.0001 - 100 wt%, suitably 0.001 - 50 wt%, of the preparation. While the dose and administration frequency vary depending on symptom, age, body weight and administration form, when it is used as an eye drop for an adult, a preparation containing a compound of formula (I') having a Rho kinase inhibitory activity in a proportion of 0.0001 - 10 w/v%, preferably 0.001 - 1 w/v%, is administered several times a day, preferably 1 - 6 times a day, by several drops, preferably 1 - 3 drops, each time. When it is used as an eye ointment, a preparation containing this compound in a proportion of 0.0001 - 10 w/w%, preferably 0.001 - 1 w/w%, can be applied several times a day, preferably 1 - 6 times a day.

Examples

[0067] The present invention is explained in detail by referring to examples and experimental examples. .

Example 1: eye drop 1 (reference example)

[0068] (+)-trans-4-(1-Aminoethyl)-1-(4-pyridylcarbamoyl)-cyclohexane 2HCl $1H_2O$ (hereinafter Compound A), which is a compound having a Rho kinase inhibitory activity, was dissolved in distilled water for injection. The pH was adjusted to 7 with sodium hydroxide and an eye drop having the following composition was prepared.

Compound A	0.5 g
Sodium dihydrogenphosphate 2 hydrate	0.1 g
Sodium chloride	0.9 g
distilled water for injection	appropriate amount
Total amount	100 ml

Example 2 : eye drop 2 (reference example)

[0069] In the same manner as in Example 1, an eye drop containing Compound A at a concentration of 0.1% was prepared.

Example 3 : eye drop 3 (reference example)

[0070] In the same manner as in Example 1, an eye drop containing Compound A at a concentration of 0.03% was prepared.

Example 4 : eye drop 4 (reference example)

[0071] In the same manner as in Example 1, an eye drop containing (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide 2HCl $6/5H_2O$ (hereinafter Compound B), which is a compound having a Rho kinase inhibitory activity, at a concentration of 0.03% was prepared.

Example 5: eye drop 5

[0072] In the same manner as in Example 1, an eye drop containing (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide 2HCl (hereinafter Compound C), which is a compound having a Rho kinase inhibitory activity, at a concentration of 0.1% was prepared.

Example 6: eye drop 6

[0073] In the same manner as in Example 5, an eye drop containing Compound C at a concentration of 0.03% was prepared.

Example 7: eye drop 7

[0074] In the same manner as in Example 1, an eye drop containing (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide 2HCl $1H_2O$ (hereinafter Compound D), which is a compound having a Rho kinase inhibitory activity, at a concentration of 0.03% was prepared.

Example 8 : tablets (reference example)

[0075] The Compound A, lactose, corn starch and crystalline cellulose were mixed, kneaded with polyvinylpyrrolidone K30 paste solution and passed through a 20-mesh sieve for granulation. After drying at 50°C for 2 hours, the granules were passed through a 24-mesh sieve, and talc and magnesium stearate were added. Using a ϕ7 mm punch, tablets weighing 120 mg per tablet were prepared.

Compound A	10.0 mg
Lactose	50.0 mg
Corn starch	20.0 mg
Crystalline cellulose	29.7 mg
Polyvinylpyrrolidone K30	5.0 mg
Talc	5.0 mg
Magnesium stearate	0.3 mg
	120.0 mg

Formulation Example 9 : Capsules (reference example)

[0076] The Compound A, lactose and corn starch were mixed, kneaded with polyvinylpyrrolidone K30 paste solution and passed through a 20-mesh sieve for granulation. After drying at 50°C for 2 hours, the granules were passed through a 24-mesh sieve and talc and magnesium stearate were added. The mixture was filled in hard capsules (No. 4) to give capsules weighing 120 mg.

Compound A	10.0 mg
Lactose	70.0 mg
Corn starch	35.0 mg
Polyvinylpyrrolidone K30	2.0 mg
Talc	2.7mg
Magnesium stearate	0.3 mg
	120.0 mg

Experimental Example 1: effect on normal intraocular pressure of coloured rabbit

Experiment method

[0077] Male Dutch coloured rabbits (body weight about 2 kg) were used. The rabbits were placed in a holding box for 3 - 5 hr a day for acclimation from one week prior to the test. The rabbits that showed steady intraocular pressure as measured by a tonometer [pneumatonograph (manufactured by Alcon Lab. Inc.)] were selected and used for the test. After measurement of the initial value of the intraocular pressure, the eye drop (50 μl) of Example 1 was instilled into one eye, and a base, which was the eye drop of Example 1 except Compound A, was instilled into the other eye in the same manner and taken as the control eye. The intraocular pressure was measured with time at 30, 60, 90 and 120 min after instillation and thereafter at 60 min intervals until the intraocular pressure returned to the initial value, and the duration of the effect was examined.

Experiment result

[0078] The effect of the eye drop of Example 1 on the normal intraocular pressure is shown in Fig. 1. When compared to the control eye at 60 min after instillation, the maximum significant intraocular pressure lowering action of 5 mmHg was observed. For 180 min after instillation, a significant intraocular pressure lowering action as compared to the control eye was found. At 360 min after instillation, the intraocular pressure was almost the same as in the control eye and returned to the initial value.

Experimental Example 2: effect on blood flow of normal optic disc of coloured rabbit

Experiment method

[0079] Male Dutch coloured rabbits (body weight about 2 kg) were used. The eye drop (50 μl) of Example 1 was instilled into one eye, and a base, which was the eye drop of Example 1 except Compound A, was instilled into the other eye in the same manner and taken as the control eye. Using a laser speckle microcirculation analyzer, the blood flow of optic disc was measured at 30, 60, 90 and 120 min after instillation and thereafter at 60 min intervals till 300 min after the instillation.

Experiment result

[0080] The effect of the eye drop of Example 1 on the optic disc blood flow kinetic is shown in Fig. 2. When compared to the control eye, a 11% blood flow increasing action was found at 30 min after instillation, and a 15% significant blood flow increasing action was found at 60 min after instillation. The blood flow increased most (18%) at 120 min after instillation. The effect gradually decreased thereafter, but a significant blood flow increasing action was observed for 180 min after the instillation as compared to the control eye. **Experimental Example 3:** effect on carbachol contraction of extracted ciliary muscle of white rabbit

Experiment method

[0081] Male Japanese white rabbits (body weight about 2 kg) were euthanized by intravenous administration of an excess pentobarbital sodium. The eyeball was enucleated immediately thereafter and preserved in a Krebs solution (NaCl:112 mM, KCl:5.9 mM, $CaCl_2$ $2H_2O$:2.0 mM, $MgCl_2$ $6H_2O$:1.2 mM, NaH_2PO_4 $2H_2O$:1.2 mM, $NaHCO_3$:25 mM, Glucose:11.5 mM). The ciliary body separated from the eyeball was hung in a Magnus bath filled with the Krebs solution and equilibrated under a 20 - 30 mg resting tension. The changes in the tension of the preparation was measured with

a transducer and recorded on a pen recorder via an amplifier. As the contraction drug, carbachol was used, and the inhibitory action on the dose dependent response of phasic contraction was studied. The test drug was (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane 2HCl $1H_2O$ (Compound A), which was added to the Magnus bath 5 min before addition of carbachol.

Experiment result

[0082] The effect of Compound A on the carbachol contraction is shown in Fig. 3. The ciliary muscle showed a dose dependent contraction by 10^{-6} - 3×10^{-4} M carbachol and Compound A showed non-competitive antagonism against carbachol contraction. The IC_{50} of Compound A against carbachol contraction was 2.8×10^{-6} M.

[0083] The contraction and relaxation of the ciliary muscle play an important role in aqueous outflow. By the relaxation of the ciliary muscle, the aqueous outflow via trabecular meshwork can be inhibited but that via uveosclera is promoted (Takeshi Yoshitomi, Neuroophthalmol. Jpn., 15(1), 76-81, 1998). The relaxation of the ciliary muscle that promotes aqueous outflow is considered to result in lowering of the intraocular pressure.

[0084] In general, 1/1000 of eye drop is said to be transferred into anterior chamber (Kouji Honda: Practical Ophthalmology, Guide of ophthalmic drug, Bunkodo Co. Ltd., Tokyo, 387-392, 1994). When 0.5% Compound A is instilled by 50 μl, 1/1000 thereof to be transferred into the anterior chamber is calculated to be 1.5×10^{-5}. Therefore, these test results are considered to show the concentration sufficiently effective in vivo as well.

Experimental Example 4: effect on normal intraocular pressure of white rabbits

Test drug

[0085] Compound A (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane 2HCl $1H_2O$ (rererence compound)

[0086] Compound B (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide 2HCl $6/5H_2O$ (rererence compound)

[0087] Compound C (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide 2HCl) Compound D (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide 2HCl $1H_2O$

[0088] In this experiment, 0.1% eye drop and 0.03% eye drop containing Compound A (each prepared in Example 2 and Example 3), 0.03% eye drop containing Compound B (prepared in Example 4), 0.1% eye drop and 0.03% eye drop containing Compound C (each prepared in Example 5 and Example 6) and 0.03% eye drop containing Compound D (prepared in Example 7) were used.

Experiment method

[0089] Japanese white rabbits (body weight about 2 kg) purchased from Japan Laboratory Animals, INC. were used. These animals were bred in a breeding chamber set to temperature 23±3°C, humidity 55±10% and fed on limited amount of 100 g a day of a solid feed (Labo R Stock, Nihon-Nosan Kogyo K.K.). They were allowed free access to tap water. The rabbits were placed in a holding box for 5 hr a day for acclimation from 2 days prior to the test. The rabbits that showed steady intraocular pressure as measured by a tonometer [pneumatonograph (manufactured by Alcon Lab. Inc.)] were selected and used for the test. After measurement of the initial value of the intraocular pressure, various eye drops (20 μl) were instilled into one eye, and a base, which was one of various eye drops except the test drug, was instilled into the other eye in the same manner and taken as the control eye. The intraocular pressure was measured with time at 30, 60, 90, 120, 150 and 180 min after instillation and thereafter at one hour intervals until the intraocular pressure returned to the initial value, and the duration of the effect was examined.

Experiment result

[0090] The effects of eye drops containing each test drug at a concentration of 0.1% on the normal intraocular pressure are shown in Fig. 4 (Examples 2, 5). The effects of eye drops containing each test drug at a concentration of 0.03% on the normal intraocular pressure are shown in Fig. 5 (Examples 3, 4) and Fig. 6 (Examples 6, 7). In every case, a significant intraocular pressure lowering effect was found. In particular, Compound A (Examples 2, 3) showed an intraocular pressure lowering effect in early stages after instillation and Compound D (Example 7) showed a marked and long lasting intraocular pressure lowering effect.

Experimental Example 5: effect on of blood flow of normal optic disc of white rabbits

Test drug

[0091] Compound A (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane 2HCl $1H_2O$ (rererence compound) Compound C (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide 2HCl In this experiment, 0.1% eye drop containing Compound A (prepared in Example 2) and 0.1% eye drop containing Compound C (prepared in Example 5) were used.

Experiment method

[0092] Japanese white rabbits (body weight about 2 kg) purchased from Japan Laboratory Animals, INC. were used. These animals were bred in a breeding chamber set to temperature 23±3°C, humidity 55±10% and fed on limited amount of 100 g a day of a solid feed (Labo R Stock, Nihon-Nosan Kogyo K.K.). They were allowed free access to tap water. In the same manner as in Example 4, each test drug was administered. Using laser speckle microcirculation analyzer, the blood flow of optic disc was measured at 30, 60, 90, 120, 150 and 180 min after instillation and thereafter at one hour intervals till 300 min after the instillation.

Experiment result

[0093] The results are shown in Fig. 7. In every case, a significant blood flow increasing action was observed from 30 min after instillation. In particular, when Compound A (Example 2) was instilled, the effect was more long-lasting.
[0094] In consideration of the results of Experimental Example 2, this optic disc blood flow increasing action was considered to be attributable to vasodilation caused by dephosphorylation of vascular smooth muscle myosin light chain due to the activation of myosin phosphatase by a compound having a Rho kinase inhibitory activity (Masayoshi Uehata, et al., Nature 389, 990-994, 1997) and the accompanying increase in ophthalmic perfusion pressure (blood pressure - intraocular pressure).

Experimental Example 6: ophthalmic disorder caused by 8-time-a-day instillation to white rabbits

Test drug

[0095] Compound A (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane2HCl $1H_2O$ (rererence compound)
[0096] Compound C (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide 2HCl
[0097] The test drugs, Compound A and Compound C, were each dissolved in the following base at a concentration of 0.125, 0.25, 0.5 and 1.0% and adjusted to pH 7 for use in this experiment.

Formulation of base

[0098]

Sodium dihydrogenphosphate 2 hydrate	0.1 g
Sodium chloride	0.9 g
Sodium hydroxide	appropriate amount
distilled water for injection	appropriate amount
Total amount	100 ml

Experiment method

[0099] Japanese white rabbits (body weight about 2 kg) purchased from Japan Laboratory Animals, INC. were used. These animals were bred in a breeding chamber set to temperature 23±3°C, humidity 55±10% and fed on limited amount of 100 g a day of a solid feed (Labo R Stock, Nihon-Nosan Kogyo K.K.). They were allowed free access to tap water. Instillation: Using a micropipet, each test drug (100 μl) was instilled into the right eye of each animal 8 times at one hour intervals. Into the left eye was instilled a base in the same manner.
[0100] Observation: anterior segment of the eye was macroscopically observed before instillation and 30 min after 2nd, 4th, 6th and 8th administrations, according to the macroscopic criteria for ocular lesions as shown in Table 1 (Naruyuki Fukui, Fumihiko Ikemoto, Gendai no Rinshou 4, 277-289, 1970). In addition, corneal staining spot was observed

before instillation and after 8th administration.

[0101] The results of macroscopic observation of the anterior segment of the eye upon administration of Compound A are shown in Table 2 and the results of macroscopic observation of the anterior segment of the eye upon administration of Compound C are shown in Table 3.

Table 1. Macroscopic criteria for ocular lesions in rabbits

Cornea	B) Edema of palpebral conjunctiva
A. Degree of opacity	· No swelling 0
· No opacity (normal) 0	· Slight edematous tendency 0.5
· Scattered or diffuse areas, details of iris clearly visible 1	· Swelling above normal 1
· Easily discernible translucent areas, details of iris slightly obscured 2	· Obvious swelling with partial eversion of lids 2
· Opalescent areas, no details of iris visible, size of pupil barely discernible 3	· Swelling with lids about half closed 3
· Opaque, iris invisible 4	· Swelling with lids about half closed to completely closed 4
B. Area of opacity	C) Redness of bulbar conjunctiva · No injection 0
· One quarter (or less) but not zero 1	· Slight vasodilatation of circumcorneal vessels 0.5
· Greater than one quarter but less than half 2	· More prominent vasodilation 1
· Greater than half but less than three quarters 3	· Marked vasodilation of vessels coursing toward the palpebral edge or the vessels tinged markedly red 2
· Greater than three quarters, up to whole area 4	D. Nictitating membrane
Iris	· No injection 0
Values	· Tendency toward vasodilation and edema 0.5
· Normal 0	· More prominent vasodilation, the palpebral edge tinged with red 1
· Folds above normal congestion, swelling circumcorneal injection (any or all of these or any combination), iris reacts to light (sluggish reaction is positive) 1	· Very marked vasodilation, the whole nictitating membrane tinged with red 2
· No reaction to light, hemorrhage, gross destruction (any or all or these) 2	E) Discharge
Conjunctiva	· No discharge · Any amount different from normal (does not include small amounts observed in inner canthus) 1
A. Redness of palpebral conjunctiva	· Discharge with moistening of the lids and hair just adjacent to lids 2
· No injection 0	· Discharge with moistening of the lids and hair, and considerable are around the eye 3
· Mucosa tinged very slightly with red, a slight vasodilation in the palpebral edge 0.5	
· Obvious injection above normal, mucosa tinged more definitely with red, prominent swelling 1	
· Mucosa tinged very markedly with red, slightly indistinct peripheral vessels 2	
· Diffuse beefy red (more severe than 2) 3	

Table 2 Scores of ocular lesions in rabbits administered with compound A (mean of three eyes)

	Item for scoring ocular lesions		Instillation				
			Before	2nd	4th	6th	8th
0.125%	Cornea	Degree	0	0	0	0	0
		Area	0	0	0	0	0
	Iris Conjunctiva	Values	0	0	0	0	0
		Palpebral redness	0	0.17	0	0.33	0.33
		Palpebral edema	0	0	0	0.33	0.50
		Bulbar redness	0	0.33	0.33	0.33	0.33
		Nictitating membrane	0	0	0	0	0.17
		Discharge	0	0	0.17	0.50	0
	Total score		0	0.50	0.50	1.99	1.33
0.25%	Cornea	Degree	0	0	0	0	0
		Area	0	0	0	0	0
	Iris Conjunctiva	Values	0	0	0	0	0
		Palpebral redness	0	0.17	0	0.33	0.33
		Palpebral edema	0	0	0	0.17	0
		Bulbar redness	0	0.50	0.50	0.50	0.83
		Nictitating membrane	0	0.17	0.50	0.50	0.50
		Discharge	0	0	0.17	0.50	0
	Total score		0	0.84	1.00	1.50	1.66
0.5%	Cornea	Degree	0	0	0	0	0
		Area	0	0	0	0	0
	Iris Conjunctiva	Values	0	0	0	0	0
		Palpebral redness	0	0.17	0.17	0.67	0.67
		Palpebral edema	0	0.17	0.17	0.83	0.67
		Bulbar redness	0.17	0.50	0.50	0.50	0.83
		Nictitating membrane	0	0	0.33	0.50	0.67
		Discharge	0	0	0.33	2.67	1.17
	Total score		0.17	0.49	1.50	5.17	4.01
1.0%	Cornea	Degree	0	0	0	0	0
		Area	0	0	0	0	0
	Iris Conjunctiva	Values	0	0	0	0	0
		Palpebral redness	0.17	0.50	0.50	0.83	2.17
		Palpebral edema	0	0.67	0.67	1.33	3.00
		Bulbar redness	0	0.50	0.50	1.17	1.50
		Nictitating membrane	0	0.17	0.50	0.67	1.67
		Discharge	0	0.33	0.67	1.67	2.33
	Total score		0.17	2.17	2.84	5.67	10.67

Table 3 Scores of ocular lesions in rabbits administered with compound C (mean of three eyes)

	Item for scoring ocular lesions		Instillation				
			Before	2nd	4th	6th	8th
0.125%	Cornea	Degree	0	0	0	0	0
		Area	0	0	0	0	0
	Iris Conjunctiva	Values	0	0	0	0	0
		Palpebral redness	0	0	0	0.17	0.33
		Palpebral edema	0	0	0	0.17	0.33
		Bulbar redness	0	0	0.50	0.17	0.50
		Nictitating membrane	0	0	0.33	0.33	0.50
		Discharge	0	0	0.17	0.50	0
	Total score		0	0	0.83	0.84	1.66
0.25%	Cornea	Degree	0	0	0	0	0
		Area	0	0	0	0	0
	Iris Conjunctiva	Values	0	0	0	0	0
		Palpebral redness	0	0	0.33	0.33	0
		Palpebral edema	0	0	0	0.17	0
		Bulbar redness	0	0.33	0.33	0.50	0.67
		Nictitating membrane	0	0.33	0.50	0.33	1.33
		Discharge	0	0	0	0.67	1.00
	Total score		0	0.66	1.50	2.83	3.00
0.5%	Cornea	Degree	0	0	0	0	0
		Area	0	0	0	0	0
	Iris Conjunctiva	Values	0	0	0.33	0	0.67
		Palpebral redness	0	0	0.33	0.33	2.00
		Palpebral edema	0	0	0.33	0.33	2.83
		Bulbar redness	0	0.50	0.50	0.67	1.00
		Nictitating membrane	0	0.50	0.33	1.00	1.00
		Discharge	0	0	0.17	1.00	2.00
	Total score		0	1.00	1.99	3.83	9.50
1.0%	Cornea	Degree	0	0	0	0	0
		Area	0	0	0	0	0
	Iris Conjunctiva	Values	0	0	0.67	1.00	1.00
		Palpebral redness	0	0.17	0.50	0.50	2.33
		Palpebral edema	0	0	0.17	0.50	3.33
		Bulbar redness	0	0.50	0.50	0.67	2.00
		Nictitating membrane	0	0.50	0.50	0.83	1.67
		Discharge	0	0	0	0.33	2.33
	Total score		0	1.17	2.34	3.83	12.66

[0102] According to the observation of corneal staining spot, the administration of Compound A at any concentration did not lead to abnormalities. In contrast, when Compound C was administered, 0.25% instillation caused abnormality in two eyes, 0. 5 and 1.0% instillations caused abnormality in all eyes at corneal epithelium. However, 0.125% instillation did not cause particular abnormality.

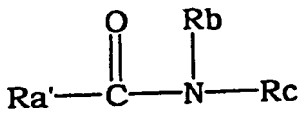
Industrial Applicability

[0103] In the agent for the prophylaxis and treatment of glaucoma of the present invention, since a compound of formula (I') having a Rho kinase inhibitory activity shows an intraocular pressure lowering effect, an optic disc blood flow improving effect and an aqueous outflow promoting effect, the agent is useful for the prophylaxis and treatment of various

types of glaucoma, such as primary open angle glaucoma, normal pressure glaucoma, hypersecretion glaucoma, ocular hypertension, acute angle closure glaucoma, chronic angle closer glaucoma, plateau iris syndrome, combined-mechanism glaucoma, steroid glaucoma, capsular glaucoma, pigmentary glaucoma, secondary glaucoma associated with amyloidosis, neovascular glaucoma, malignant glaucoma .

Claims

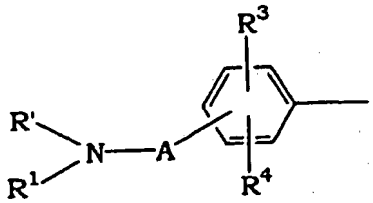
1. A compound having a Rho kinase inhibitory activity of the following formula (I')



(I')

wherein

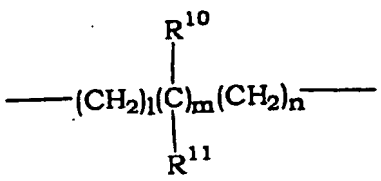
Ra' is a group of the formula



(b')

wherein

R' is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, or cycloalkyl having 3 to 7 carbon atoms, cycloalkylalkyl wherein the cycloalkyl moiety has 3 to 7 carbon atoms and the alkyl moiety is linear or branched alkyl having 1 to 6 carbon atoms, phenyl or aralkyl wherein the alkyl moiety is alkyl, having 1 to 4 carbon atoms, which optionally has a substituent on the ring,
R^1 is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, or cycloalkyl having 3 to 7 carbon atoms, cycloalkylalkyl wherein the cycloalkyl moiety has 3 to 7 carbon atoms and the alkyl moiety is linear or branched alkyl having 1 to 6 carbon
R^2 atoms, phenyl or aralkyl wherein the alkyl moiety is alkyl having 1 to 4 carbon atoms, which optionally has a substituent on the ring, or R' and R^1 in combination form, together with the adjacent nitrogen atom, a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom, is hydrogen or linear or branched alkyl having 1 to 10 carbon atoms,
R^3 and R^4 are the same or different and each is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, aralkyl wherein the alkyl moiety is alkyl having 1 to 4 carbon atoms, halogen, nitro, amino, alkylamino, acylamino, hydroxy, alkoxy, aralkyloxy, cyano, acyl, mercapto, alkylthio, aralkylthio, carboxy, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or azide, and
A is a group of the formula



(c)

wherein R^{10} and R^{11} are the same or different and each is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, haloalkyl, aralkyl wherein the alkyl moiety is alkyl having 1 to 4 carbon atoms, hydroxyalkyl,

carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl having 3 to 7 carbon atoms in combination and 1, m and n are each 0 or an integer of 1-3,
Rb is a hydrogen, a linear or branched alkyl having 1 to 10 carbon atoms, an aralkyl wherein the alkyl moiety is alkyl having 1 to 4 carbon atoms, an aminoalkyl or a mono- or dialkylaminoalkyl; and
Rc is an optionally substituted hetereocycle containing nitrogen,

an optical an cis-trans isomer thereof and/or a pharmaceutically acceptable acid addition salt thereof, for use in the prophylaxis and treatment of glaucoma.

2. The compound for use as in claim 1, wherein the compound is (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridine-4-yl)-4-(1-aminoethyl)benzamide and/or a pharmaceutically acceptable acid addition salt thereof.

3. The compound for use as in claim 1 or 2 wherein the compound is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridine-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof.

4. The compound for use as in claims 1 to 3 wherein the pharmaceutically acceptable acid addition salt is a salt, wherein the acid is an inorganic acid selected from hydrochloric acid, hydrobromic acid, and sulfuric acid or an organic acid such as methanesulfonic acid, fumaric acid, maleic acid, mandelic acid, citric acid, tartaric acid, and salicylic acid.

5. The compound for use as in claims 1 to 4, wherein the acid addition salt is a hydrochloric acid addition salt.

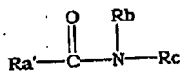
6. The compound for use as in claim 1 for administration to a local site in the eye.

7. The compound for use as in claim 6 for administration in the form of an eye drop.

8. An agent comprising the compound of anyone of claims 1 to 7 for use in the prophylaxis and treatment of glaucoma.

Patentansprüche

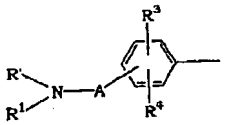
1. Verbindung, die eine Rho-Kinase-hemmende Aktivität aufweist, mit der folgenden Formel (I'):



(I')

wobei

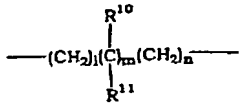
Ra' eine Gruppe der Formel



(b')

ist; wobei R' Folgendes ist: Wasserstoff, lineares oder verzweigtes Alkyl mit 1 bis 10 Kohlenstoffatomen oder Cycloalkyl mit 3 bis 7 Kohlenstoffatomen, Cycloalkylalkyl, wobei die Cycloalkyl-Struktureinheit 3 bis 7 Kohlenstoffatome aufweist und die Alkyl-Struktureinheit lineares oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist, Phenyl oder Aralkyl, wobei die Alkyl-Struktureinheit Alkyl mit 1 bis 4 Kohlenstoffatomen ist, gegebenenfalls mit einem Substituenten am Ring;
R^1 Folgendes ist: Wasserstoff, lineares oder verzweigtes Alkyl mit 1 bis 10 Kohlenstoffatomen oder Cycloalkyl mit 3 bis 7 Kohlenstoffatomen, Cycloalkylalkyl, wobei die Cycloalkyl-Struktureinheit 3 bis 7 Kohlenstoffatome aufweist und die Alkyl-Struktureinheit lineares oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist, Phenyl oder Aralkyl, wobei die Alkyl-Struktureinheit Alkyl mit 1 bis 4 Kohlenstoffatomen ist, gegebenenfalls mit einem Substituenten am Ring, oder R' und R' in Kombination zusammen mit dem benachbarten Stickstoffatom eine

Gruppe ergeben, die einen Heterocyclus bildet, der gegebenenfalls im Ring ein Sauerstoffatom, Schwefelatom oder gegebenenfalls substituiertes Stickstoffatom aufweist;
R^2 Wasserstoff oder lineares oder verzweigtes Alkyl mit 1 bis 10 Kohlenstoffatomen ist;
R^3 und R^4 gleich oder verschieden sind und jeweils Wasserstoff, lineares oder verzweigtes Alkyl mit 1 bis 10 Kohlenstoffatomen, Aralkyl, wobei die Alkyl-Struktureinheit Alkyl mit 1 bis 4 Kohlenstoffatomen ist, Halogen, Nitro, Amino, Alkylamino, Acylamino, Hydroxy, Alkoxy, Aralkyloxy, Cyano, Acyl, Mercapto, Alkylthio, Aralkylthio, Carboxy, Alkoxycarbonyl, Carbamoyl, Alkylcarbamoyl oder Azid sind; und
A eine Gruppe der Formel


(c)

ist, wobei R^{10} and R^{11} gleich oder verschieden sind und jeweils Wasserstoff, lineares oder verzweigtes Alkyl mit 1 bis 10 Kohlenstoffatomen, Halogenalkyl, Aralkyl wobei die Alkyl-Struktureinheit Alkyl mit 1 bis 4 sind oder Kohlenstoffatomen ist, Hydroxyalkyl, Carboxy oder Alkoxycarbonyl sind oder R^{10} und R^{11} eine Gruppe ergeben, die in Kombination Cycloalkyl mit 3 bis 7 Kohlenstoffatomen bildet, und l, m und n jeweils 0 oder eine ganze Zahl von 1 bis 3 sind;
Rb Wasserstoff, lineares oder verweigtes Alkyl mit 1 bis 10 Kohlenstoffatomen Aralkyl wobei die Alkyl-Struktureinheit Alkyl mit 1 bis 4 Kohlenstoffatomen ist, Aminoalkyl oder Mono- oder Dialkylaminoalkyl ist; und
Rc ein gegebenenfalls substituierter Heterocyclus ist, der Stickstoff enthält;

ein optisches oder cis-trans-Isomer davon und/oder ein pharmazeutisch annehmbares Säureadditionssalz davon Verwendung dei der Prophylaxe und Behandlung von Glaukom.

2. Verbindung zur Verwendung gemäß Anspruch 1, wobei es sich bei der Verbindung um (R)-(+)-N-(4-Pyridyl)-4-(1-aminoethyl)benzamid, R)-(+)-N-(1H-Pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzmid oder ein pharmazeutisch annehmbares Säureadditionssalz davon handelt.

3. Verbindung zur Verwendung gemäß Anspruch 1 oder 2, wobei es sich bei der Verbindung um (R)-(+)-N-(1H-Pyrrolo [2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamid oder ein pharmazeutisch annehmbares Säureadditionssalz davon handelt.

4. Verbindung zur Verwendung gemäß Anspruch 1 bis 3, wobei das pharmazeutisch annehmbare Säureadditionssalz ein Salz ist, bei dem die Säure eine anorganische Säure, die aus Chlorwasserstoffsäure, Bromwasserstoffsäure und Schwefelsäure ausgewählt ist, oder eine organische Säure, wie Methansulfonsäure, Fumarsäure, Maleinsäure, Mandelsäure, Zitronensäure, Weinsäure und Salicylsäure, ist.

5. Verbindung zur Verwendung gemäß Anspruch 1 bis 4, wobei das Säureadditionssalz ein Hydrochlorid-Säureadditionssalz ist.

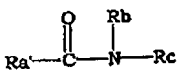
6. Verbindung zur Verwendung gemäß Anspruch 1 zur Verabreichung an eine lokale Stelle im Auge.

7. Verbindung zur Verwendung gemäß Anspruch 6 zur Verabreichung in Form von Augentropfen.

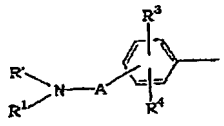
8. Mittel, das die Vebindung gemäß einem der Ansprüche 1 bis 7 umfasst, zur Verwendung bei der Prophylaxe und Behandlung von Glaukom.

Revendications

1. Composé possédant une activité inhibitrice de la Rho kinase de formule (I') suivante


(I')

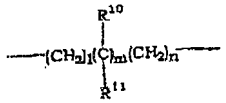
dans laquelle Ra' représente un groupe de formule



(b')

dans laquelle

R' représente un atome d'hydrogène, un groupe alkyle linéaire ou ramifié contenant 1 à 10 atomes de carbone, ou cycloalkyle contenant 3 à 7 atomes de carbone, cycloalkylalkyle où le radical cycloalkyle contient 3 à 7 atomes de carbone et le radical alkyle est un alkyle linéaire ou ramifié contenant 1 à 6 atomes de carbone, phényle ou aralkyle où le radical alkyle est un alkyle contenant 1 à 4 atomes de carbone, qui a éventuellement un substituant sur le cycle,
R^1 représente un atome d'hydrogène, un groupe alkyle linéaire ou ramifié contenant 1 à 10 atomes de carbone, ou cycloalkyle contenant 3 à 7 atomes de carbone, cycloalkylalkyle où le radical cycloalkyle contient 3 à 7 atomes de carbone et le radical alkyle est un alkyle linéaire ou ramifié contenant 1 à 6 atomes de carbone, phényle ou aralkyle où le radical alkyle est un alkyle contenant 1 à 4 atomes de carbone, qui a éventuellement un substituant sur le cycle, ou R' et R^1 en combinaison forment, conjointement avec l'atome d'azote adjacent, un groupe formant un hétérocycle ayant éventuellement, dans le cycle, un atome d'oxygène, un atome de soufre ou un atome d'azote éventuellement substitué,
R^2 représente un atome d'hydrogène ou un groupe alkyle linéaire ou ramifié contenant 1 à 10 atomes de carbone,
R^3 et R^4 sont identiques ou différents et chacun représente un atome d'hydrogène, un groupe alkyle linéaire ou ramifié contenant 1 à 10 atomes de carbone, aralkyle où le radical alkyle est un alkyle contenant 1 à 4 atomes de carbone, un atome d'halogène, un groupe nitro, amino, alkylamino, acylamino, hydroxy, alcoxy, aralkyloxy, cyano, acyle, mercapto, alkylthio, aralkylthio, carboxy, alcoxycarbonyle, carbamoyle, alkylcarbamoyle ou azide, et
A est un groupe de formule



(c)

dans laquelle R^{10} et R^{11} sont identiques ou différents et chacun représente un atome d'hydrogène, un groupe alkyle linéaire ou ramifié contenant 1 à 10 atomes de carbone, halogénoalkyle, aralkyle où le radical alkyle est un alkyle contenant 1 à 4 atomes de carbone, hydroxyalkyle, carboxy ou alcoxycarbonyle, ou R^{10} et R^{11} représentent un groupe qui forme un groupe cycloalkyle contenant 3 à 7 atomes de carbone en combinaison et 1, m et n valent chacun 0 ou un nombre entier de 1 à 3,
Rb représente un atome d'hydrogène, un groupe alkyle linéaire ou ramifié contenant 1 à 10 atomes de carbone, aralkyle où le radical alkyle est un alkyle contenant 1 à 4 atomes de carbone, aminoalkyle ou mono- ou dialkylaminoalkyle ; et
Rc représente un hétérocycle éventuellement substitué contenant de l'azote,
un isomère optique ou *cis-trans* de celui-ci et/ou un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci,
pour une utilisation dans la prophylaxie et le traitement du glaucome.

2. composé pour une utilisation selon la revendication 1, où le composé est le (R)-(+)-N-(4-pyridyl)-4-(1-aminoéthyl) benzamide, le (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-y1)-4-(1-amino-éthyl)-benzamide et/ou un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci.

3. Composé pour une utilisation selon la revendication 1 ou 2, où le composé est le (R)-(+)-N-(1H-pyrrolo[2,3-b)pyridin-4-yl)-4-(l-amino-éthyl)-benzamide ou un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci.

4. Composé pour une utilisation selon les revendications 1 à 3, où le sel d'addition d'acide pharmaceutiquement acceptable est un sel, où l'acide est un acide inorganique choisi parmi l'acide chlorhydrique, l'acide bromhydrique et l'acide sulfurique ou un acide organique tel que l'acide méthane sulfonique, l'acide fumarique, l'acide maléique,

l'acide mandélique, l'acide citrique, l'acide tartrique et l'acide salicylique.

5. Composé pour une utilisation selon les revendications 1 à 4, où le sel d'addition d'acide est un sel d'addition d'acide chlorhydrique.

6. Composé pour une utilisation selon la revendication 1, pour une administration à un site local dans l'oeil.

7. Composé pour une utilisation selon la revendication 6, pour une administration sous la forme d'une goutte pour les yeux.

8. Agent comprenant le composé selon l'une quelconque des revendications 1 à 7 pour une utilisation dans la prophylaxie et le traitement du glaucome.

FIG. 1

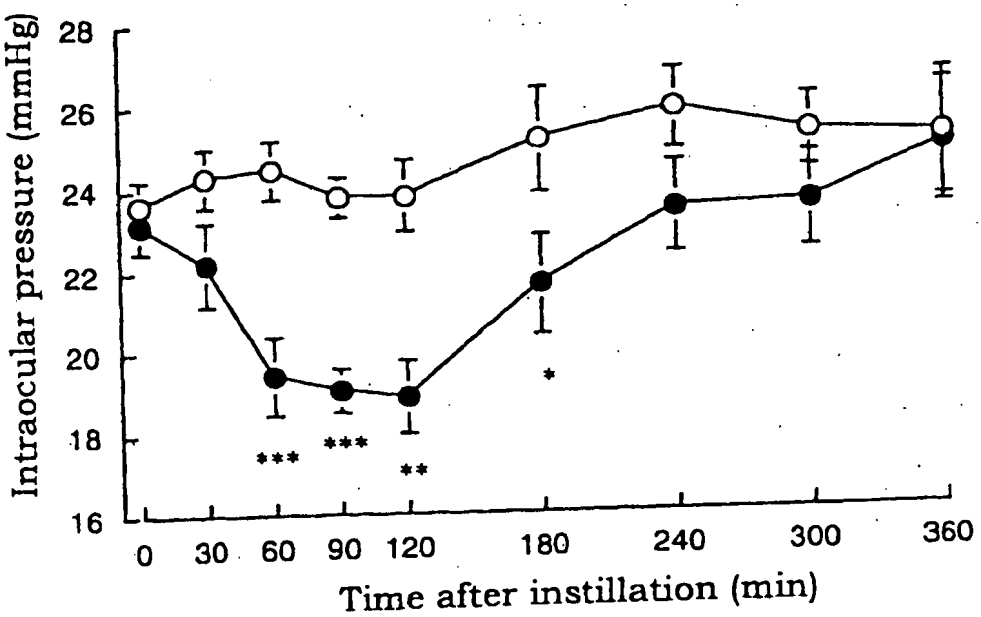

Intraocular pressure (mmHg)
28
26
24
22
20
18
16
0
30
60
90
120
180
240
300
360
Time after instillation (min)
***
***
**
*

FIG. 2

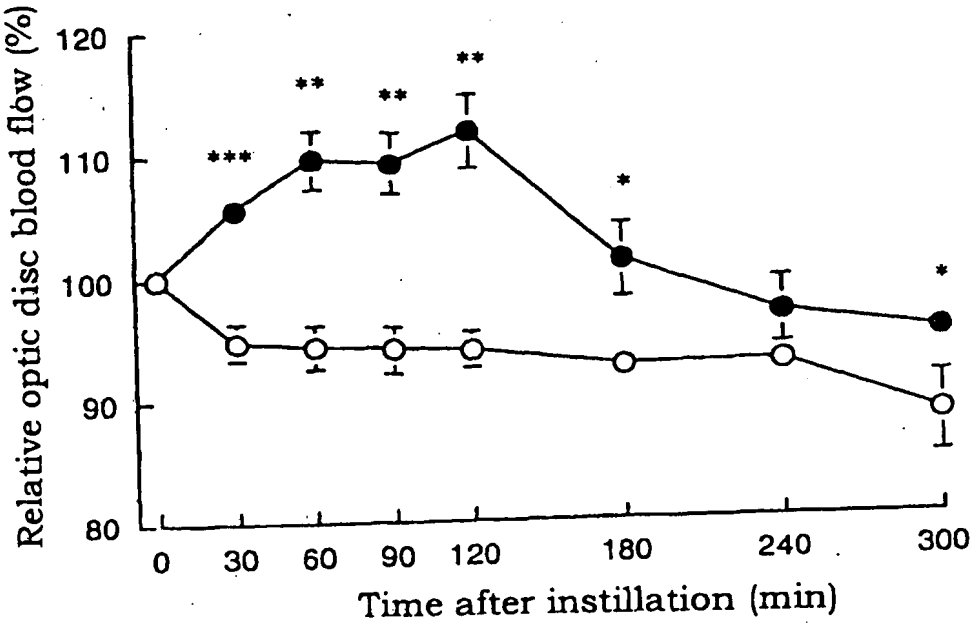

Relative optic disc blood flow (%)
120
110
100
90
80
***
**
**
**
*
*
0
30
60
90
120
180
240
300
Time after instillation (min)

FIG. 3

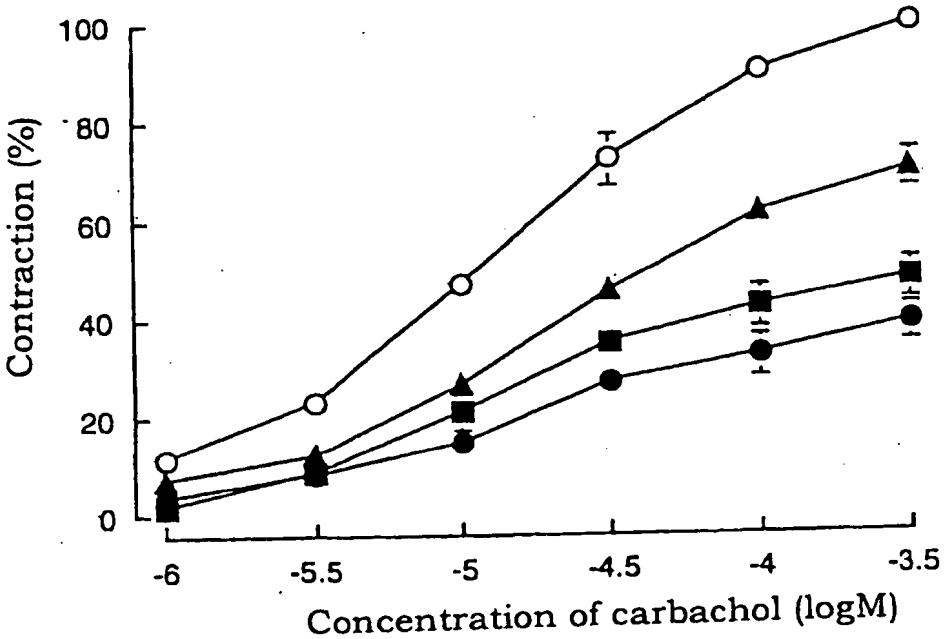

100
80
60
40
20
0
Contraction (%)
-6
-5.5
-5
-4.5
-4
-3.5
Concentration of carbachol (logM)

FIG. 4

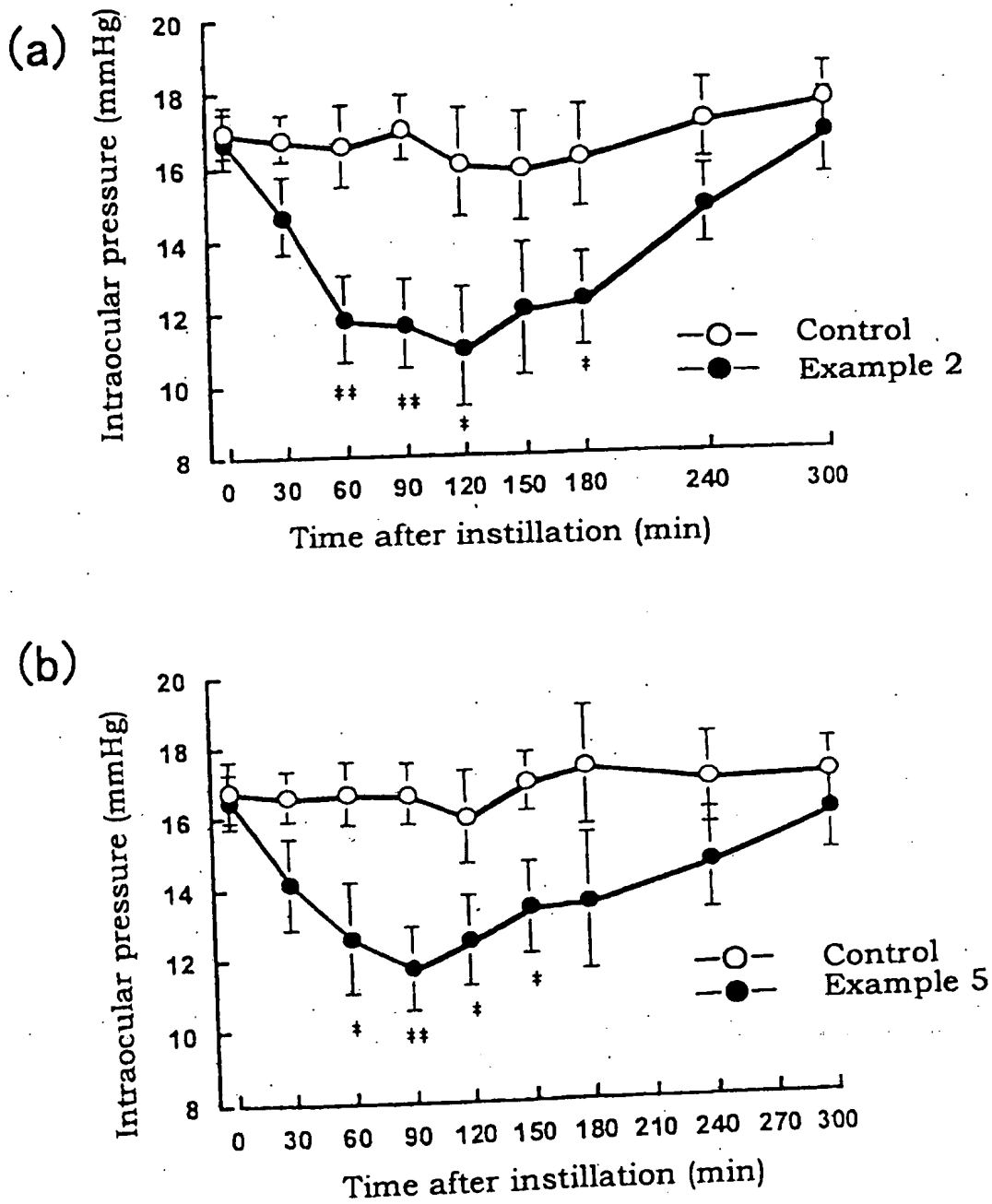
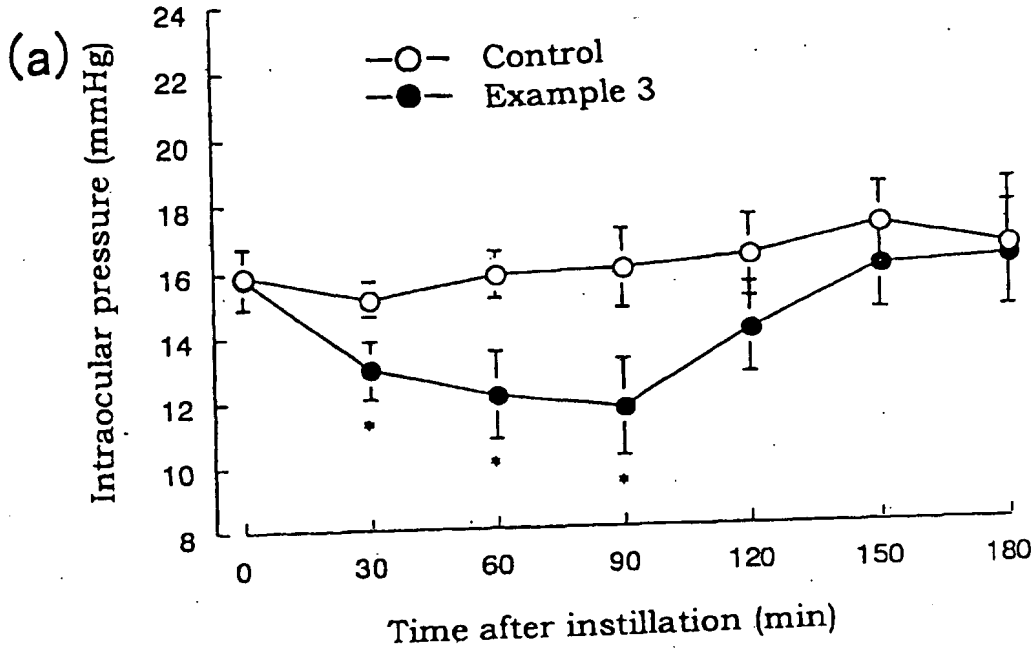

(a)
Intraocular pressure (mmHg)
20
18
16
14
12
10
8
0 30 60 90 120 150 180 240 300
Time after instillation (min)
Control
Example 2
(b)
Intraocular pressure (mmHg)
20
18
16
14
12
10
8
0 30 60 90 120 150 180 210 240 270 300
Time after instillation (min)
Control
Example 5

FIG. 5


(a)
Control
Example 3
Intraocular pressure (mmHg)
24
22
20
18
16
14
12
10
8
0
30
60
90
120
150
180
Time after instillation (min)

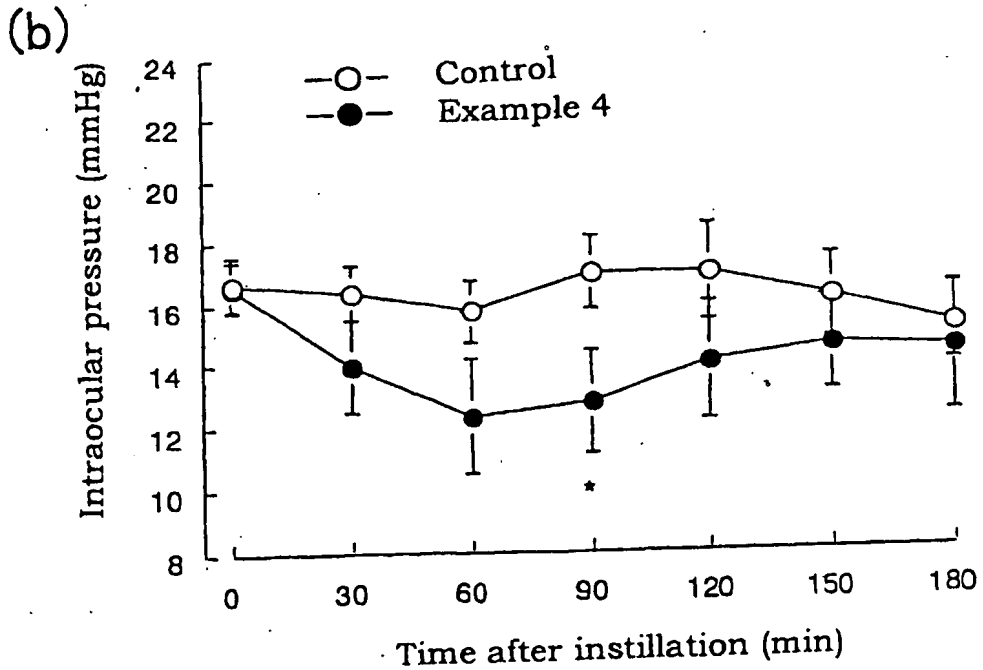
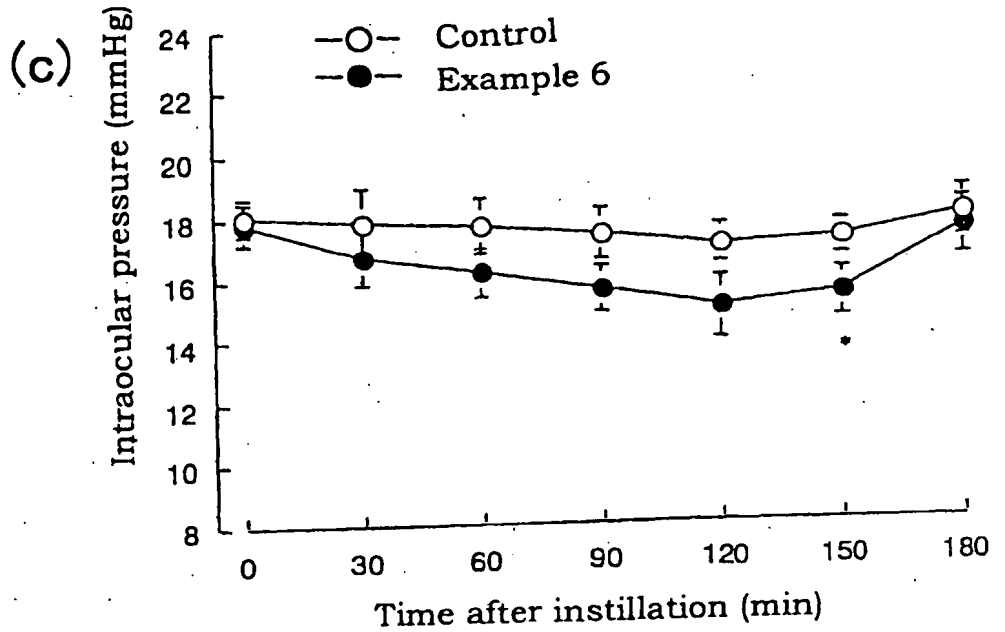

(b)
Control
Example 4
Intraocular pressure (mmHg)
24
22
20
18
16
14
12
10
8
0
30
60
90
120
150
180
Time after instillation (min)

FIG. 6


(c)
Control
Example 6
Intraocular pressure (mmHg)
24
22
20
18
16
14
12
10
8
0
30
60
90
120
150
180
Time after instillation (min)

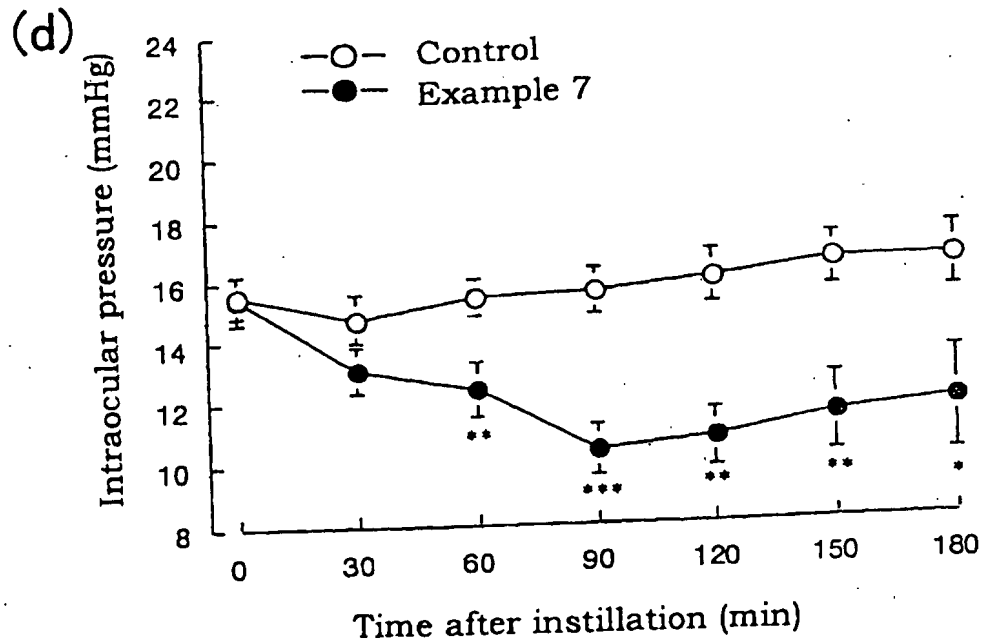
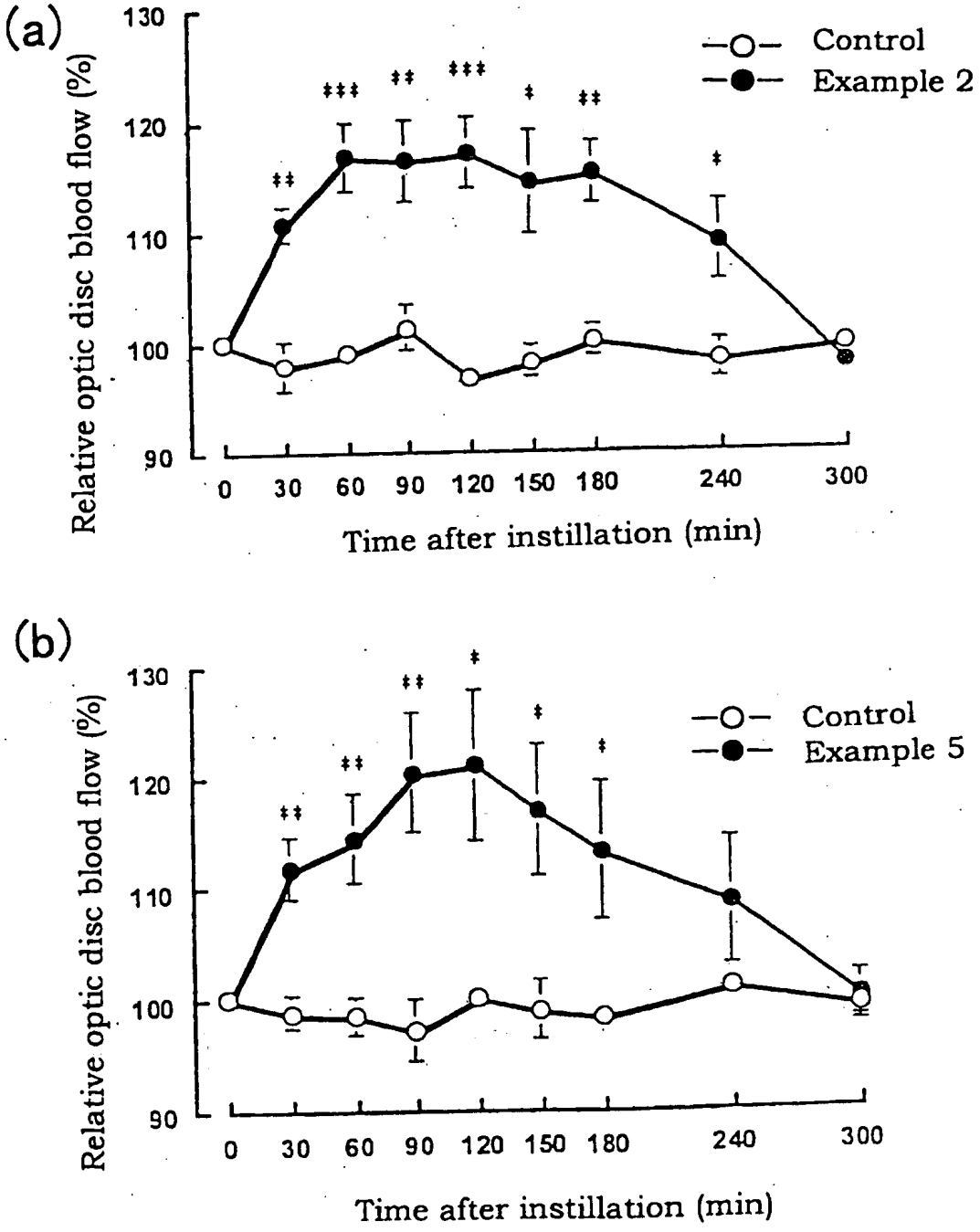

(d)
Control
Example 7
Intraocular pressure (mmHg)
24
22
20
18
16
14
12
10
8
0
30
60
90
120
150
180
Time after instillation (min)

FIG. 7


(a)
Relative optic disc blood flow (%)
130
120
110
100
90
0
30
60
90
120
150
180
240
300
Time after instillation (min)
Control
Example 2
(b)
Relative optic disc blood flow (%)
130
120
110
100
90
0
30
60
90
120
150
180
240
300
Time after instillation (min)
Control
Example 5

REFERENCES CITED IN THE DESCRIPTION

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