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(54) Agent for prophylaxis and treatment of asthenopia and pseudomyopia

Verbindung zur Vorbeugung und Behandlung von Augen-Asthenopie und Pseudomyopie

Agent pour prévenir et traiter l'asthénopie et la pseudomyopie

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WO-A-97/30701 **WO-A-98/06433**

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- **UEHATA M ET AL: "Calcium sensitization of smooth muscle mediated by a Rho-associated protein kinase in hypertension" NATURE, NATURE PUBLISHING GROUP, LONDON, GB, vol. 389, 30 October 1997 (1997-10-30), pages 990-994, XP002131752 ISSN: 0028-0836**

EP 1 459 742 B1

Description

Technical Field

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

Background Art

[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 al-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 (WO98/06433). 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] DATABASE WPI week 199530 Derwent Publications Ltd., London, GB; AN 1995-227293 XP002458451 & JP 07 133225 A (DAIICHI PHARM CO LTD) 23 May 1995 (1995-05-23) and DATABASE WPI Week 199732 Derwent Publications Ltd., London, GB; AN 1997-347410 XP002458452 & JP 09 143099 A (SANTEN PHARM CO LTD) 3 June 1997 (1997-06-03) disclose the ability of ciliary muscle tension relaxing agents treat pseudomyopia and asthenopia.

[0008] WO-A-97/30701 discloses that H-7(1-(5-isoqinolinyl-sulfonyl)-2-methylpiperazine) has been shown to inhibit pilocarpine induced contraction of ciliary muscle.

Disclosure of the Invention

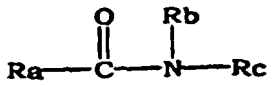
[0009] The present invention aims at solving the above-mentioned problems and discloses a novel agent for the prophylaxis and treatment of glaucoma, which is superior in a prophylactic and therapeutic effect on glaucoma.

[0010] The present inventors have conducted intensive studies and found that inasmuch as the compound having a

Rho kinase inhibitory activity inhibits contraction of ciliary muscle, it is useful as an agent for the prophylaxis and treatment of asthenopia and pseudomyopia caused by sustained abnormal tension of ciliary muscle which resulted in the completion of the present invention.

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

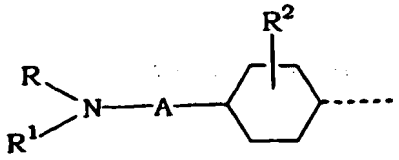
(1) A compound of the following formula (I):



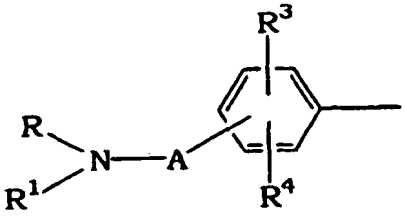
(I)

wherein

Ra is a group of the formula

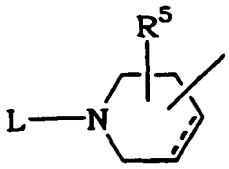


(a)



(b)

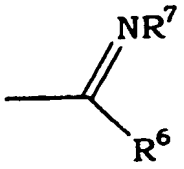
or



(c)

in the formulas (a) and (b),

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 a linear or branched alkyl having 1 to 6 carbon atoms, phenyl or aralkyl wherein the alkyl has 1 to 4 carbon atoms, which optionally has a substituent on the ring, or a group of the formula



(d)

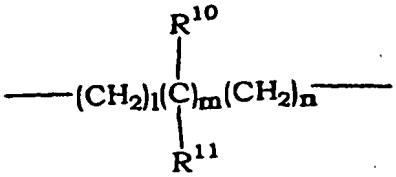
wherein R6 is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms or formula: $-NR^8R^9$ wherein R^8 and R^9 are the same or different and each is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, aralkyl wherein the alkyl has 1 to 4 carbon atoms or phenyl, R^7 is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, aralkyl wherein the alkyl has 1 to 4 carbon atoms, phenyl, nitro or cyano, or R^6 and R^7 in combination show a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

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 a linear or branched alkyl having 1 to 6 carbon atoms, phenyl or aralkyl wherein the alkyl has 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,

R^2 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 has 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

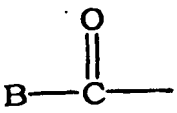


(e)

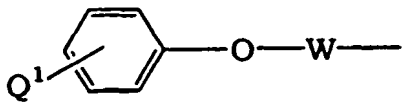
wherein R^{10} and R^{11} are the same or different and each is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, haloalkyl, aralkyl wherein the alkyl has 1 to 4 carbon atoms, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination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

in the formula (c),

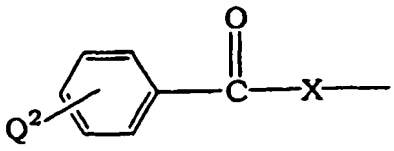
L is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, aminoalkyl, mono- or dialkylaminoalkyl, tetrahydrofurfuryl, carbamoylalkyl, phthalimidoalkyl, amidino or a group of the formula



(f)

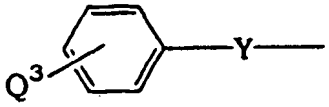


(g)



(h)

or



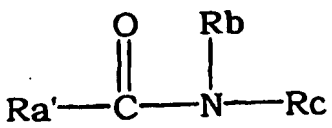
(i)

wherein B is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, alkoxy, aralkyl wherein the alkyl has 1 to 4 carbon atoms, aralkyloxy, aminoalkyl, hydroxyalkyl, alkanoyloxyalkyl, alkoxycarbonylalkyl, α-aminobenzyl, furyl, pyridyl, phenyl, phenylamino, styryl, or imidazopyridyl,
Q^1 is hydrogen, halogen, hydroxy, aralkyloxy or thienylmethyl,
W is alkylene,
Q^2 is hydrogen, halogen, hydroxy or aralkyloxy,
X is alkylene,
Q^3 is hydrogen, halogen, hydroxy, alkoxy, nitro, amino, 2,3-dihydrofuryl or 5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl;
and Y is a single bond, alkylene or alkenylene, and

in the formula (c),
a broken line is a single bond or a double bond, and

R^5 is a hydrogen, hydroxy, alkoxy, alkoxycarbonyloxy, alkanoyloxy or aralkyloxycarbonyloxy;
Rb is a hydrogen, a linear or branched alkyl having 1 to 10 carbon atoms, an aralkyl wherein the alkyl has 1 to 4 carbon atoms, an aminoalkyl or a mono- or dialkylaminoalkyl; and
Rc is an optionally substituted heterocycle containing nitrogen, an optical cis-trans isomer thereof or a pharmaceutically acceptable acid addition salt thereof, for use in the prophylaxis and treatment of asthenopia or pseudomyopia.

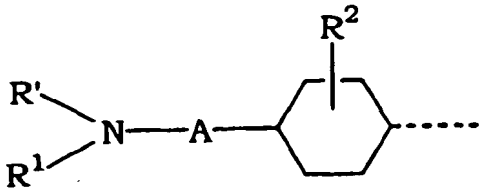
(2) The compound of (1) above having the following formula (I')



(I')

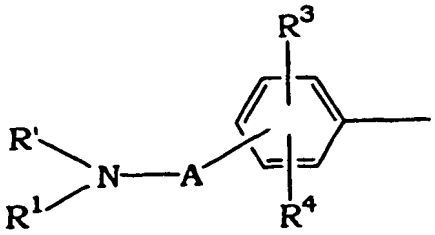
wherein

Ra' is a group of the formula



(a')

or



(b')

wherein

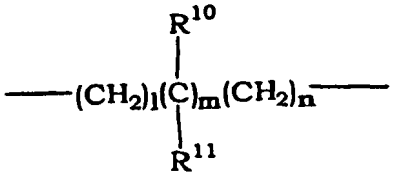
R' is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, or cycloalkyl having 3 to 7 carbon atoms, cycloalkylalkyl wherein the cycloalkyl moiety has 3 to 7 carbon atoms and the alkyl moiety is a linear or branched alkyl having 1 to 6 carbon atoms, phenyl or aralkyl wherein the alkyl has 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 a linear or branched alkyl having 1 to 6 carbon atoms, phenyl or aralkyl wherein the alkyl has 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 optinally substituted nitrogen atom,

R^2 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 has 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, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl 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 has 1 to 4 carbon atoms, an aminoalkyl or a mono- or dialkylaminoalkyl; and

Rc is an optionally substituted heterocycle containing nitrogen, an optical cis-trans isomer thereof or a pharmaceutically acceptable acid addition salt thereof.

(3) The compound of (2) above, wherein the compound is (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane, (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide, (R)-(+)-N-(4-pyri-

dyl)-4-(1-aminoethyl)benzamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof.

(4) The compound of (2) above for administration to a local site on the eye.

(5) The compound of (2) above for administration in an eye drop form to the eye.

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

(7) The compound of (2) above, wherein the compound is a hydrochloric acid salt of (R)-(+)-N-(1H-pyrrolo[2,3-b] pyridin-4-yl)-4-(1-aminoethyl)benzamide.

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

[0012] Fig. 1 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, O 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.

Detailed Description of the Invention

[0013] 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.

[0014] The compound having a Rho kinase inhibitory activity used as an active ingredient in the present invention are the compounds of the formula (I). Of these, a compound of the formula (I') is more preferably used. In the present invention, said compound having one kind of Rho kinase inhibitory activity can be used alone or, where necessary, several kinds of the compounds can be used.

[0015] In the present specification, each symbol of the formulas (I) and (I') is defined as follows.

[0016] Alkyl at R, 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.

[0017] Cycloalkyl at R, R' and R^1 has 3 to 7 carbon atoms and is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl.

[0018] Cycloalkylalkyl at R, 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), 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 and the like.

[0019] Aralkyl at R, 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

[0020] The substituent of optionally substituted cycloalkyl, cycloalkylalkyl, phenyl and aralkyl on the ring at R, R' and R^1 is halogen (e.g., chlorine, bromine, fluorine and iodine), alkyl (same as alkyl at R, 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, R' and R^1) or haloalkyl (alkyl at R, 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), nitro, amino, cyano, azide.

[0021] The group formed by R and R' or 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, R' and R^1.

[0022] Alkyl at R^2 is as defined for R, R' and R^1.

[0023] Halogen, alkyl, alkoxy and aralkyl at R^3 and R^4 are as defined for R, R' and R^1.

[0024] 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).

[0025] 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.

[0026] 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.

[0027] 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.

[0028] 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.

[0029] 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.

[0030] 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.

[0031] 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.

[0032] Alkoxy at R^5 is as defined for R, R' and R^1.

[0033] Alkoxycarbonyloxy at R^5 is that wherein the alkoxy moiety is linear or branched alkoxy having 1 to 6 carbon atoms, which is exemplified by methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, isopropoxycarbonyloxy, butoxycarbonyloxy, isobutoxycarbonyloxy, sec-butoxycarbonyloxy, tert-butoxycarbonyloxy, pentyloxycarbonyloxy, hexyloxycarbonyloxy.

[0034] Alkanoyloxy at R^5 is that wherein the alkanoyl moiety is alkanoyl having 2 to 6 carbon atoms, which is exemplified by acetyloxy, propionyloxy, butyryloxy, valeryloxy, pivaloyloxy.

[0035] Aralkyloxycarbonyloxy at R^5 is that wherein the aralkyl moiety is aralkyl having C_1-C_4 alkyl, which is exemplified by benzyloxycarbonyloxy, 1-phenylethyloxycarbonyloxy, 2-phenylethyloxycarbonyloxy, 3-phenylpropyloxycarbonyloxy, 4-phenylbutyloxycarbonyloxy.

[0036] Alkyl at R^6 is as defined for R, R' and R^1; alkyl at R^8 and R^9 is as defined for R, R' and R^1; and aralkyl at R^8 and R^9 is as defined for R, R' and R^1.

[0037] Alkyl at R^7 is as defined for R, R' and R^1 and aralkyl at R^7 is as defined for R, R' and R^1.

[0038] The group formed by R^6 and R^7 in combination, which forms a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom, is imidazol-2-yl, thiazol-2-yl, oxazol-2-yl, imidazolin-2-yl, 3,4,5,6-tetrahydropyridin-2-yl, 3,4,5,6-tetrahydropyrimidin-2-yl, 1,3-oxazolin-2-yl, 1,3-thiazolin-2-yl or optionally substituted benzoimidazol-2-yl, benzothiazol-2-yl, benzoxazol-2-yl and the like having a substituent such as halogen, alkyl, alkoxy, haloalkyl, nitro, amino, phenyl, aralkyl. As used herein, halogen, alkyl, alkoxy, haloalkyl and aralkyl are as defined for R, R' and R^1.

[0039] The substituent of the above-mentioned optionally substituted nitrogen atom is exemplified by alkyl, aralkyl, haloalkyl. As used herein, alkyl, aralkyl and haloalkyl are as defined for R, R' and R^1.

[0040] 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, R' and R^1; haloalkyl and alkoxycarbonyl at R^{10} and R^{11} are as defined for R, R' and R^1; aralkyl at R^{10} and R^{11} is as defined for R, R' and R^1; and cycloalkyl formed by R^{10} and R^{11} in combination is the same as cycloalkyl at R, R' and R^1.

[0041] Alkyl at L is as defined for R, R' and R^1.

[0042] Aminoalky at L 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, 6-aminohexyl.

[0043] Mono- or dialkylaminoalkyl at L 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, 2-diethylaminoethyl.

[0044] Carbamoylalkyl at L is linear or branched alkyl having 1 to 6 carbon atoms substituted by carbamoyl, which is exemplified by carbamoylmethyl, 2-carbamoylethyl, 1-carbamoylethyl, 3-carbamoylpropyl, 4-carbamoylbutyl, 5-car-

bamoylpentyl, 6-carbamoylhexyl.

[0045] Phthalimidoalkyl at L is linear or branched alkyl having 1 to 6 carbon atoms, which is substituted by phthalimide. Examples thereof include phthalimidomethyl, 2-phthalimidoethyl, 1-phthalimidoethyl, 3-phthalimidopropyl, 4-phthalimidobutyl, 5-phthalimidopentyl, 6-phthalimidohexyl.

[0046] Alkyl at B is as defined for R, R' and R^1.

[0047] Alkoxy at B is as defined for R, R' and R^1.

[0048] Aralkyl at B is as defined for R, R' and R^1.

[0049] Aralkyloxy at B is as defined for R^3 and R^4.

[0050] Aminoalkyl at B is as defined for L.

[0051] Hydroxyalkyl at B is as defined for R^{10} and R^{11}.

[0052] Alkanoyloxyalkyl at B is that wherein linear or branched alkyl having 1 to 6 carbon atoms is substituted by alkanoyloxy having alkanoyl moiety having 2 to 6 carbon atoms, which is exemplified by acetyloxymethyl, propionyloxymethyl, butyryloxymethyl, valeryloxymethyl, pivaloyloxymethyl, acetyloxyethyl, propionyloxyethyl, butyryloxyethyl, valeryloxyethyl, pivaloyloxyethyl.

[0053] Alkoxycarbonylalkyl at B is that wherein linear or branched alkyl having 1 to 6 carbon atoms is substituted by alkoxycarbonyl having alkoxy moiety having 1 to 6 carbon atoms, which is exemplified by methoxycarbonylmethyl, ethoxycarbonylmethyl, propoxycarbonylmethyl, isopropoxycarbonylmethyl, butoxycarbonylmethyl, isobutoxycarbonylmethyl, sec-butoxycarbonylmethyl, tert-butoxycarbonylmethyl, pentyloxycarbonylmethyl, hexyloxycarbonylmethyl, methoxycarbonylethyl, ethoxycarbonylethyl, propoxycarbonylethyl, isopropoxycarbonylethyl, butoxycarbonylethyl, isobutoxycarbonylethyl, sec-butoxycarbonylethyl, tert-butoxycarbonylethyl, pentyloxycarbonylethyl, hexyloxycarbonylethyl.

Halogen at Q^1, Q^2 and Q^3 is as defined for R, R' and R^1.

[0054] Aralkyloxy at Q^1 and Q^2 is as defined for R^3 and R^4.

[0055] Alkoxy at Q^3 is as defined for R, R' and R^1.

[0056] Alkylene at W, X and Y is linear or branched alkylene having 1 to 6 carbon atoms, which is exemplified by methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethylene.

[0057] Alkenylene at Y is linear or branched alkenylene having 2 to 6 carbon atoms, which is exemplified by vinylene, propenylene, butenylene, pentenylene.

[0058] Alkyl at Rb is as defined for R, R' and R^1.

[0059] Aralkyl at Rb is as defined for R, R' and R^1.

[0060] Aminoalkyl at Rb is as defined for L.

[0061] Mono- or dialkylaminoalkyl at Rb is as defined for L.

[0062] 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.

[0063] 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.

[0064] As used herein, the substituent of the optionally substituted hydrazino includes alkyl, aralkyl, nitro, cyano, wherein alkyl and aralkyl are as defined for R, R' and R^1 and exemplified by methylhydrazino, ethylhydrazino, benzylhydrazino.

[0065] The compound of the formula (I) [inclusive of the compounds of the formula (I')] is exemplified by the following compounds.

(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-benzyloxyoarboxamidomethylcyclohexyl-carbonyl)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)cylohexane
(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-aminomethylcyclohexane-carboxamide
(108) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-aminomethyl-cyclohexanecarboxamide
(109) (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)cyclohexanecarboxamide
(110) trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-amino-1-methylethyl)cyclohexanecarboxamide

(111) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-aminomethyl-cyclohexanecarboxamide
(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-aminomethylcyclohexane-carboxamide
(120) trans-N-(7H-imidazo[4,5-d]pyrimidin-6-yl)-4-aminomethyl-cyclohexanecarboxamide
(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-aminomethyl-cyclohexanecarboxamide
(125) trans-N-(4-pyridazinyl)-4-aminomethylcyclohexanecarboxamide
(126) trans-N-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-aminomethyl-cyclohexanecarboxamide
(127) trans-N-(2-amino-4-pyridyl)-4-aminomethylcyclohexane-carboxamide
(128) trans-N-(thieno[2,3-d]pyrimidin-4-yl)-4-aminomethyl-cyclohexanecarboxamide
(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-aminomethyl-cyclohexanecarboxamide
(133) trans-N-(2,6-diamino-4-pyrimidyl)-4-aminomethylcyclohexane-carboxamide
(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-aminomethylcyclohexane-carboxamide
(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-aminomethylcyclohexane-carboxamide
(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-guanidinomethyl-cyclohexanecarboxamide
(143) trans-N-(1H-pyrazolo[3,4-b]pyridin-4-yl)-4-guanidinomethyl-cyclohexanecarboxamide
(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-guanidinomethylcyclohexane-carboxamide
(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-guanidinomethyl-benzamide
(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

[0066] Preferred are compounds (80), (109), (110), (112), (115), (142), (143), (144), (145), (153), (157), (163), (165), (166) and (179).

[0067] 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, 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.

[0068] 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.

[0069] 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.

[0070] A compound having a Rho kinase inhibitory activity, particularly, a compound 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 and the like. 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-mecha-

nism glaucoma, steroid glaucoma, capsular glaucoma, pigmentary glaucoma, secondary glaucoma associated with amyloidosis, neovascular glaucoma, malignant glaucoma.

[0071] The agent for the prophylaxis and treatment of asthenopia and pseudomyopia 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.

[0072] 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.

[0073] 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.

[0074] 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).

[0075] When preparing a liquid preparation, an additive, such as sodium chloride, glucose, sorbitol, glycerol, olive oil, propylene glycol, ethyl alcohol, is used.

[0076] The liquid preparation may be, for example, injection, eye drop.

[0077] 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.

[0078] 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.

[0079] The buffer may be, for example, phosphate buffer, borate buffer, citrate buffer, tartrate buffer, acetate buffer, amino acid.

[0080] The stabilizer may be, for example, sodium edetate, citric acid.

[0081] The wetting agent may be, for example, glycerol.

[0082] The emulsifier may be, for example, polyvinylpyrrolidone.

[0083] The suspending agent may be, for example, hydroxypropylmethylcellulose, methylcellulose.

[0084] The surfactant may be, for example, polysorbate 80, polyoxyethylene hydrogenated castor oil.

[0085] 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.

[0086] 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.

[0087] The thickener may be, for example, hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, salts thereof.

[0088] When in use as an eye drop, pH is preferably adjusted generally to about 4 - 9, preferably about 6 - 8.5.

[0089] When the preparation is an eye ointment, an ointment base (e.g., petrolatum, lanolin, plastibase), a preservative (e.g., benzalkonium chloride, p-hydroxybenzoate, chlorobutanol), are appropriately selected and used for production.

[0090] The agent for the prophylaxis and treatment of asthenopia and pseudomyopia 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 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

[0091] The present invention is explained in detail by referring to examples and experimental examples.

Example 1: eye drop 1

[0092] (+)-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

[0093] 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

[0094] 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

[0095] 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

[0096] 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

[0097] 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

[0098] 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

[0099] 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

[0100] 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 carbachol contraction of extracted ciliary muscle of white rabbit

Experiment method

[0101] 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

[0102] The effect of Compound A on the carbachol contraction is shown in Fig. 1. 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.

[0103] 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.

[0104] 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 2: ophthalmic disorder caused by 8-time-a-day instillation to white rabbits

Test drug

Compound A (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane 2HCl $1H_2O$

Compound-C (R)-(+)-N-(4-pyridyl)-4-(1-aminoethyl)benzamide 2HCl

[0105] 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	
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

[0106] 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.
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.

[0107] 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
			C) Redness of bulbar conjunctiva	
B.	Area of opacity		• 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	

(continued)

	• Greater than three quarters, up to whole area	4	markedly red	2
Iris			D. Nictitating membrane	
Values			• No injection	0
	• Normal	0	• Tendency toward vasodilation and edema	0.5
	• Folds above normal congestion, swelling circumcorneal injection (any or all of these or any combination), iris reacts to light (sluggish reaction is positive)	1	• More prominent vasodilation, the palpebral edge tinged with red	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	
			• No discharge	6
Conjunctiva			• 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	Values	0	0	0	0	0
	Conjunctiva	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

(continued)

	Item for scoring ocular lesions		Instillation Before	2nd	4th	6th	8th
0.25%	Cornea	Degree	0	0	0	0	0
		Area	0	0	0	0	0
	Iris	Values	0	0	0	0	0
	Conjunctiva	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	Values	0	0	0	0	0
	Conjunctiva	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	Values	0	0	0	0	0
	Conjunctiva	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	Values	0	0	0	0	0
	Conjunctiva	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

(continued)

	Item for scoring ocular lesions		Instillation Before	2nd	4th	6th	8th
0.25%	Cornea	Degree	0	0	0	0	0
		Area	0	0	0	0	0
	Iris	Values	0	0	0	0	0
	Conjunctiva	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	Values	0	0	0.33	0	0.67
	Conjunctiva	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	Values	0	0	0.67	1.00	1.00
	Conjunctiva	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	0.67	2.00
		Discharge	0	0	0	0.33	2.33
	Total score		0	1.17	2.34	3.83	12.66

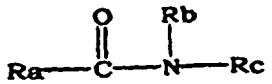
[0108] According to the observation of corneal staining spot, the administration of Compound A at any concentration did not lead to abnormalities. In contrast, when Compound C was administered, 0.25% instillation caused abnormality in two eyes, 0. 5 and 1.0% instillations caused abnormality in all eyes at corneal epithelium. However, 0.125% instillation did not cause particular abnormality.

Industrial Applicability

[0109] Inasmuch as the compound having a Rho kinase inhibitory activity inhibits contraction of ciliary muscle, it is useful as an agent for the prophylaxis and treatment of asthenopia and pseudomyopia caused by sustained abnormal tension of ciliary muscle.

Claims

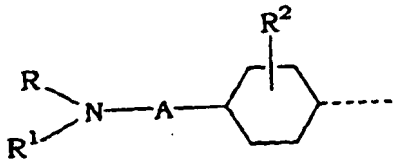
1. A compound having a Rho kinase inhibitory activity of the following formula (I):



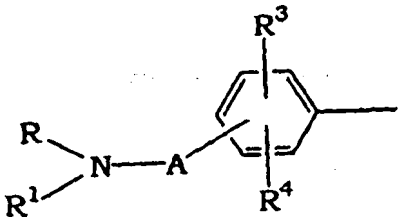
(I)

wherein

Ra is a group of the formula

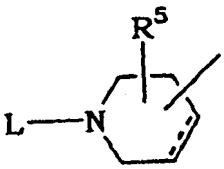


(a)



(b)

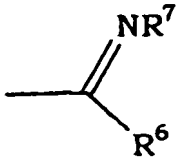
or



(c)

in the formulas (a) and (b),

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 a linear or branched alkyl having 1 to 6 carbon atoms, phenyl or aralkyl wherein the alkyl has 1 to 4 carbon atoms, which optionally has a substituent on the ring, or a group of the formula



(d)

wherein R6 is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms or formula: $-NR^8R^9$ wherein R^8 and R^9 are the same or different and each is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, aralkyl wherein the alkyl has 1 to 4 carbon atoms or phenyl, R^7 is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, aralkyl wherein the alkyl has 1 to 4 carbon atoms, phenyl, nitro or cyano, or R^6 and R^7 in

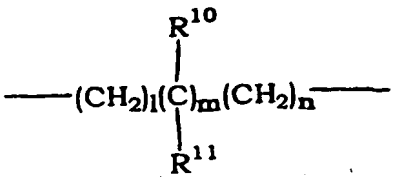
combination show a group forming a heterocycle optionally having, in the ring, oxygen atom, sulfur atom or optionally substituted nitrogen atom,

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 a linear or branched alkyl having 1 to 6 carbon atoms, phenyl or aralkyl wherein the alkyl has 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,

R^2 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 has 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

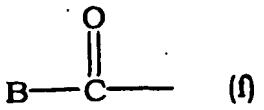


(e)

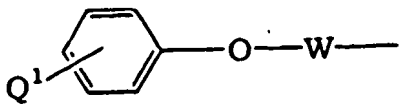
wherein R^{10} and R^{11} are the same or different and each is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, haloalkyl, aralkyl wherein the alkyl has 1 to 4 carbon atoms, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl in combination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

in the formula (c),

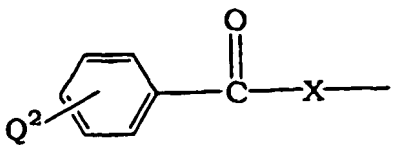
L is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, aminoalkyl, mono- or dialkylaminoalkyl, tetrahydrofurfuryl, carbamoylalkyl, phthalimidoalkyl, amidino or a group of the formula



(f)

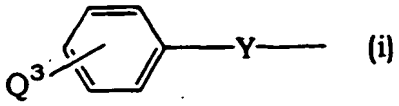


(g)



(h)

or



(i)

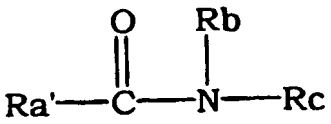
wherein B is hydrogen, linear or branched alkyl having 1 to 10 carbon atoms, alkoxy, aralkyl wherein the alkyl has 1 to 4 carbon atoms, aralkyloxy, aminoalkyl, hydroxyalkyl, alkanoyloxyalkyl, alkoxycarbonylalkyl, α-aminobenzyl, furyl, pyridyl, phenyl, phenylamino, styryl or imidazopyridyl,
Q^1 is hydrogen, halogen, hydroxy, aralkyloxy or thienylmethyl,
W is alkylene,
Q^2 is hydrogen, halogen, hydroxy or aralkyloxy,
X is alkylene,
Q^3 is hydrogen, halogen, hydroxy, alkoxy, nitro, amino, 2,3-dihydrofuryl or 5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl; and Y is a single bond, alkylene or alkenylene, and

in the formula (c),
a broken line is a single bond or a double bond, and

R^5 is a hydrogen, hydroxy, alkoxy, alkoxycarbonyloxy, alkanoyloxy or aralkyloxycarbonyloxy;
Rb is a hydrogen, a linear or branched alkyl having 1 to 10 carbon atoms, an aralkyl wherein the alkyl has 1 to 4 carbon atoms, an aminoalkyl or a mono- or dialkylaminoalkyl; and
Rc is an optionally substituted heterocycle containing nitrogen,

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

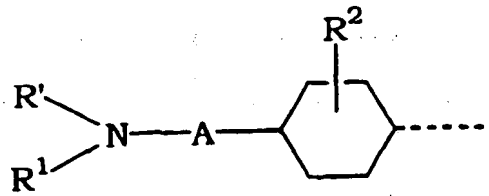
2. The compound for use as in claim 1 having the following formula (I')



(I')

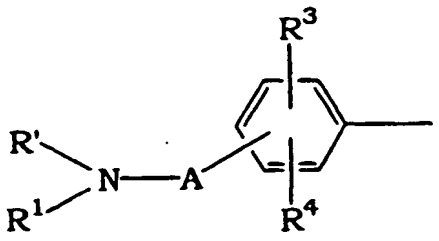
wherein

Ra' is a group of the formula



(a')

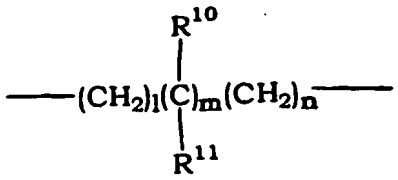
or



(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 a linear or branched alkyl having 1 to 6 carbon atoms, phenyl or aralkyl wherein the alkyl has 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 a linear or branched alkyl having 1 to 6 carbon atoms, phenyl or aralkyl wherein the alkyl has 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 optinally substituted nitrogen atom,
R^2 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 has 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, hydroxyalkyl, carboxy or alkoxycarbonyl, or R^{10} and R^{11} show a group which forms cycloalkyl 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 has 1 to 4 carbon atoms, an aminoalkyl or a mono- or dialkylaminoalkyl; and
Rc is an optionally substituted heterocycle containing nitrogen,

an optical cis-trans isomer thereof or a pharmaceutically acceptable acid addition salt thereof.

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

4. The compound for use as in claim 2 for administration to a local site on the eye.

5. The compound for use as in claim 2 for administration in an eye drop form to the eye.

6. The compound for use as in claim 2, wherein the compound is (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-ami-

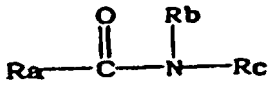
noethyl)benzamide or a pharmaceutically acceptable acid addition salt thereof.

7. The compound for use as in claim 2, wherein the compound is a hydrochloric acid salt of (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide.

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

Patentansprüche

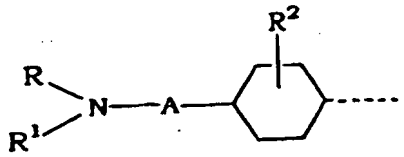
1. Verbindung, die eine Rho-Kinase-hemmende Aktivität aufweist, mit der folgenden Formel (I):



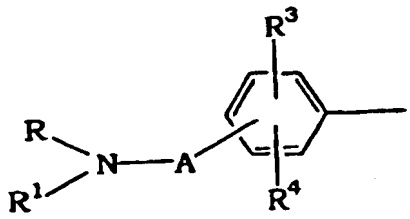
(I)

wobei

Ra eine Gruppe der Formel

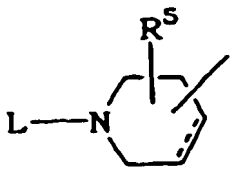


(a)



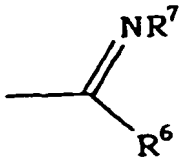
(b)

oder



(c)

ist;
wobei in den Formeln (a) und (b)
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 das Alkyl 1 bis 4 Kohlenstoffatome aufweist, gegebenenfalls mit einem Substituenten am Ring, oder eine Gruppe der Formel



(d)

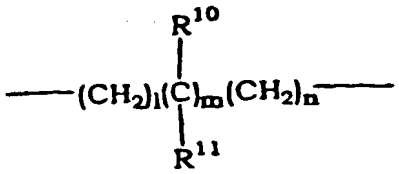
wobei R^6 Wasserstoff, lineares oder verzweigtes Alkyl mit 1 bis 10 Kohlenstoffatomen ist oder der Formel $-NR^3R^9$ entspricht, wobei R^8 und R^9 gleich oder verschieden sind und jeweils Wasserstoff, lineares oder verzweigtes Alkyl mit 1 bis 10 Kohlenstoffatomen, Aralkyl, wobei das Alkyl 1 bis 4 Kohlenstoffatome aufweist, oder Phenyl sind, R^1 Wasserstoff, lineares oder verzweigtes Alkyl mit 1 bis 10 Kohlenstoffatomen, Aralkyl, wobei das Alkyl 1 bis 4 Kohlenstoffatome aufweist, Phenyl, Nitro oder Cyano ist oder R^6 und R^7 in Kombination eine Gruppe ergeben, die einen Heterocyclus bildet, der gegebenenfalls im Ring ein Sauerstoffatom, Schwefelatom oder gegebenenfalls substituiertes Stickstoffatom aufweist;

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 das Alkyl 1 bis 4 Kohlenstoffatome aufweist, gegebenenfalls mit einem Substituenten am Ring, oder R und R^1 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 das Alkyl 1 bis 4 Kohlenstoffatome aufweist, 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

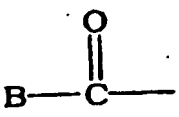


(e)

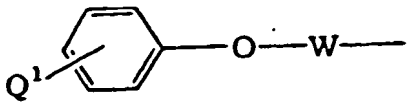
ist, wobei R^{10} und R^{11} gleich oder verschieden sind und jeweils Wasserstoff, lineares oder verzweigtes Alkyl mit 1 bis 10 Kohlenstoffatomen, Halogenalkyl, Aralkyl, wobei das Alkyl 1 bis 4 Kohlenstoffatome aufweist, Hydroxyalkyl, Carboxy oder Alkoxycarbonyl sind oder R^{10} und R^{11} eine Gruppe ergeben, die in Kombination Cycloalkyl bildet, und l, m und n jeweils 0 oder eine ganze Zahl von 1 bis 3 sind;

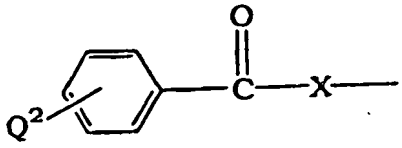
in Formel (c)

L Wasserstoff, lineares oder verzweigtes Alkyl mit 1 bis 10 Kohlenstoffatomen, Aminoalkyl, Mono- oder Dialkylaminoalkyl, Tetrahydrofurfuryl, Carbamoylalkyl, Phthalimidoalkyl, Amidino oder eine Gruppe der Formel

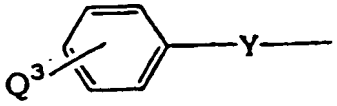


(f)


(g)


(h)

oder


(i)

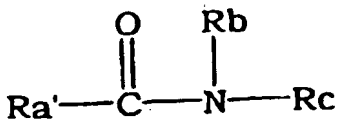
ist, wobei B Wasserstoff, lineares oder verzweigtes Alkyl mit 1 bis 10 Kohlenstoffatomen, Alkoxy, Aralkyl, wobei das Alkyl 1 bis 4 Kohlenstoffatome aufweist, Aralkyloxy, Aminoalkyl, Hydroxyalkyl, Alkanoyloxyalkyl, Alkoxycarbonylalkyl, α-Aminobenzyl, Furyl, Pyridyl, Phenyl, Phenylamino, Styryl oder Imidazopyridyl ist;
Q^1 Wasserstoff, Halogen, Hydroxy, Aralkyloxy oder Thienylmethyl ist;
W Alkylen ist;
Q^2 Wasserstoff, Halogen, Hydroxy oder Aralkyloxy ist;
X Alkylen ist;
Q^3 Wasserstoff, Halogen, Hydroxy, Alkoxy, Nitro, Amino, 2,3-Dihydrofuryl oder 5-Methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl ist; und
Y eine Einfachbindung, Alkylen oder Alkenylen ist; und

in Formel (c)
eine gebrochene Linie eine Einfachbindung oder eine Doppelbindung ist; und
R^5 Wasserstoff, Hydroxy, Alkoxy, Alkoxycarbonyloxy, Alkanoyloxy oder Aralkyloxycarbonyloxy ist;

Rb Wasserstoff, lineares oder verzweigtes Alkyl mit 1 bis 10 Kohlenstoffatomen, Aralkyl, wobei das Alkyl 1 bis 4 Kohlenstoffatome aufweist, Aminoalkyl oder Mono- oder Dialkylaminoalkyl ist; und
Rc ein gegebenenfalls substituierter Heterocyclus ist, der Stickstoff enthält;

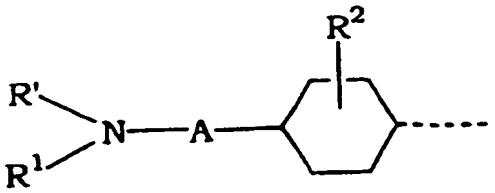
ein optisches oder cis-trans-Isomer davon oder ein pharmazeutisch annehmbares Säureadditionssalz davon zur Verwendung bei der Prophylaxe und Behandlung von Asthenopie oder Pseudomyopie.

2. Verbindung zur Verwendung gemäß Anspruch 1 mit der folgenden Formel (I')


(I')

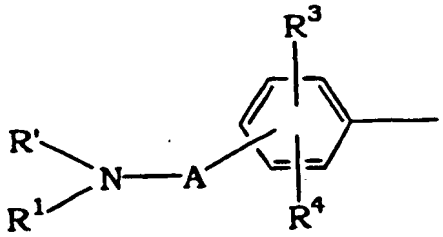
wobei

Ra' eine Gruppe der Formel



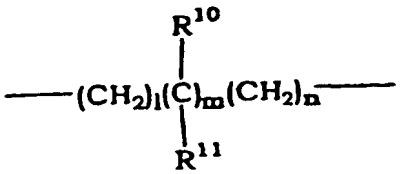
(a')

oder



(b')

ist;
wobei
R' 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 das Alkyl 1 bis 4 Kohlenstoffatome aufweist, gegebenenfalls mit einem Substituenten am Ring, ist;
R^1 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 das Alkyl 1 bis 4 Kohlenstoffatome aufweist, gegebenenfalls mit einem Substituenten am Ring, ist oder R' und R^1 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 das Alkyl 1 bis 4 Kohlenstoffatome aufweist, 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



(e)

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

ein optisches oder cis-trans-Isomer davon oder ein pharmazeutisch annehmbares Säureadditionssalz davon.

3. Verbindung zur Verwendung gemäß Anspruch 2, wobei es sich bei der Verbindung um (+)-trans-4-(1-Aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexan, (+)-trans-N-(1H-Pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)-cyclohexancarboxamid, (R)-(+)-N-(4-Pyridyl)-4-(1-aminoethyl)benzamid, (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 2 zur Verabreichung an eine lokale Stelle am Auge.

5. Verbindung zur Verwendung gemäß Anspruch 2 zur Verabreichung in Augentropfenform an das Auge.

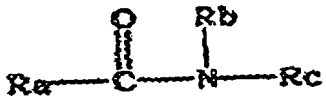
6. Verbindung zur Verwendung gemäß Anspruch 2, wobei es sich bei der Verbindung um (R)-(+)-N-(1H-Pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamid oder ein pharmazeutisch annehmbares Säureadditionssalz davon handelt.

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

8. Mittel, das die Verbindung gemäß einem der Ansprüche 1 bis 7 umfasst, zur Verwendung bei der Prophylaxe und Behandlung von Asthenopie oder Pseudomyopie.

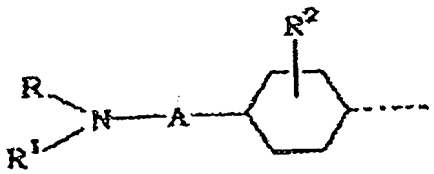
Revendications

1. Composé ayant une activité inhibitrice de kinase Rho répondant à la formule (I) suivante :

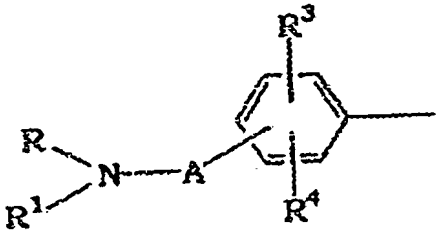


(I)

dans laquelle
Ra est un groupe de formule

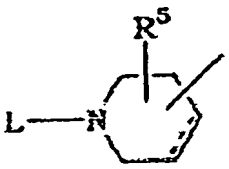


(a)



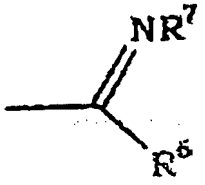
(b)

ou



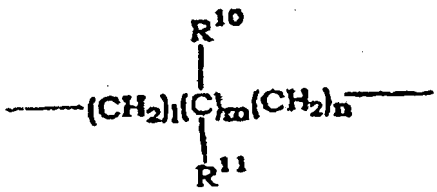
(c)

dans les formules (a) et (b),
R est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone, ou un cycloalkyle ayant de 3 à 7 atomes de carbone, un cycloalkylalkyle dans lequel le fragment cycloalkyle a de 3 à 7 atomes de carbone et le fragment alkyle est un alkyle linéaire ou ramifié ayant de 1 à 6 atomes de carbone, un phényle ou aralkyle dans lequel l'alkyle a de 1 à 4 atomes de carbone, qui porte éventuellement un substituant sur le cycle, ou un groupe de formule



(d)

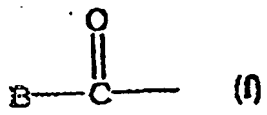
dans laquelle R^6 est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone ou répond à la formule : $-NR^8R^9$ dans laquelle R^8 et R^9 sont identiques ou différents et chacun est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone, un aralkyle dans lequel l'alkyle a de 1 à 4 atomes de carbone ou un phényle, R^7 est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone, un aralkyle dans lequel l'alkyle a de 1 à 4 atomes de carbone, un phényle, nitro ou cyano, ou R^6 et R^7 en combinaison représentent 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^1 est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone, ou un cycloalkyle ayant de 3 à 7 atomes de carbone, un cycloalkylalkyle dans lequel le fragment cyclo-alkyle a de 3 à 7 atomes de carbone et le fragment alkyle est un alkyle linéaire ou ramifié ayant de 1 à 6 atomes de carbone, un phényle ou aralkyle dans lequel l'alkyle a de 1 à 4 atomes de carbone, qui porte éventuellement un substituant sur le cycle, ou R et R^1 en combinaison forment, 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 est un atome d'hydrogène ou un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone,
R^3 et R^4 sont identiques ou différents et chacun est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone, un aralkyle dans lequel l'alkyle a de 1 à 4 atomes de carbone, un atome d'halogène, un nitro, amino, alkylamino, acylamino, hydroxy, alcoxy, aralkyloxy, cyano, acyle, mercapto, alkylthio, aralkylthio, carboxy, alcoxycarbonyle, carbamoyle, alkyl-carbamoyle ou azoture, et
A est un groupe de formule



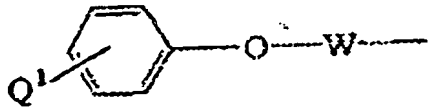
(e)

dans laquelle R^{10} et R^{11} sont identiques ou différents et chacun est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone, un halogénoalkyle, un aralkyle dans lequel l'alkyle a de 1 à 4 atomes de carbone, un hydroxyalkyle, carboxy ou alcoxycarbonyle, ou R^{10} et R^{11} en combinaison représentent un groupe qui forme un cycloalkyle et l, m, et n sont chacun 0 ou un nombre entier de 1 à 3,
dans la formule (c),
L est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone, un aminoalkyle, un

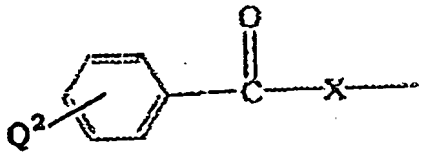
mono- ou dialkylaminoalkyle, tétrahydrofurfuryle, carbamoylalkyle, phtalimidoalkyle, amidino ou un groupe de formule



(f)

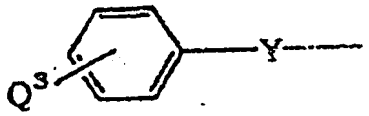


(g)



(h)

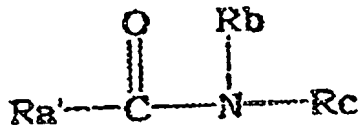
ou



(i)

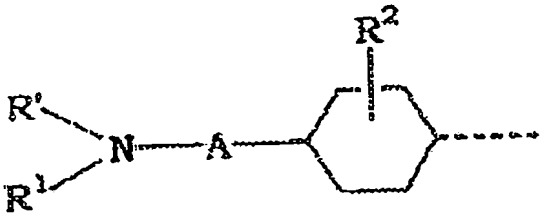
dans laquelle
B est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone, un alcoxy, aralkyle dans lequel l'alkyle a de 1 à 4 atomes de carbone, un aralkyloxy, aminoalkyle, hydroxyalkyle, alcanoyloxyalkyle, alcoxycarbonylalkyle, α-aminobenzyle, furyle, pyridyle, phényle, phénylamino, styryle, ou imidazopyridyle,
Q^1 est un atome d'hydrogène, un atome d'halogène, un hydroxy, aralkyloxy ou thiénylméthyle,
W est un alkylène,
Q^2 est un atome d'hydrogène, un atome d'halogène, un hydroxy ou aralkyloxy,
X est un alkylène,
Q^3 est un atome d'hydrogène, un atome d'halogène, un hydroxy, alcoxy, nitro, amino, 2,3-dihydrofuryle ou 5-méthyl-3-oxo-2,3,4,5-tétrahydropyridazin-6-yle ;
et Y est une liaison simple, un alkylène ou alcénylène, et
dans la formule (c),
une ligne brisée est une liaison simple ou une double liaison, et
R^5 est un atome d'hydrogène, un hydroxy, alcoxy, alcoxycarbonyloxy, alcanoyloxy, alcanoyloxy ou aralkyloxycarbonyloxy ;
Rb est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone, un aralkyle dans lequel l'alkyle a de 1 à 4 atomes de carbone, un aminoalkyle ou un mono- ou dialkylaminoalkyle ; et
Rc est un hétérocycle éventuellement substitué contenant un atome d'azote, un isomère optique ou cis-trans de celui-ci ou un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci,
pour son utilisation pour prévenir ou traiter l'asthénopie ou la pseudo-myopie.

2. Composé pour son utilisation comme dans la revendication 1, répondant à la formule (I') suivante



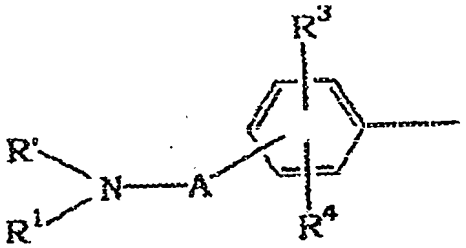
(I')

dans laquelle
Ra' est un groupe de formule



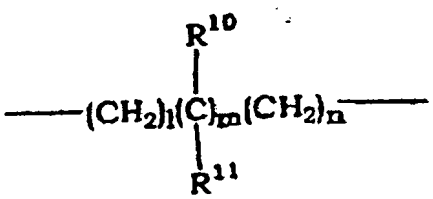
(a')

ou



(b')

dans laquelle
R' est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone, ou un cycloalkyle ayant de 3 à 7 atomes de carbone, un cycloalkylalkyle dans lequel le fragment cycloalkyle a de 3 à 7 atomes de carbone et le fragment alkyle est un alkyle linéaire ou ramifié ayant de 1 à 6 atomes de carbone, un phényle ou aralkyle dans lequel l'alkyle a de 1 à 4 atomes de carbone, qui porte éventuellement un substituant sur le cycle,
R^1 est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone, ou un cycloalkyle ayant de 3 à 7 atomes de carbone, un cycloalkylalkyle dans lequel le fragment cyclo-alkyle a de 3 à 7 atomes de carbone et le fragment alkyle est un alkyle linéaire ou ramifié ayant de 1 à 6 atomes de carbone, un phényle ou aralkyle dans lequel l'alkyle a de 1 à 4 atomes de carbone, qui porte éventuellement un substituant sur le cycle, ou
R' et R^1 en combinaison forment, 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 est un atome d'hydrogène ou un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone,
R^3 et R^4 sont identiques ou différents et chacun est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone, un aralkyle dans lequel l'alkyle a de 1 à 4 atomes de carbone, un atome d'halogène, un nitro, amino, alkylamino, acylamino, hydroxy, alcoxy, aralkyloxy, cyano, acyle, mercapto, alkylthio, aralkylthio, carboxy, alcoxycarbonyle, carbamoyle, alkyl-carbamoyle ou azoture, et
A est un groupe de formule



(e)

dans laquelle

R^{10} et R^{11} sont identiques ou différents et chacun est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone, un halogénoalkyle, aralkyle, hydroxyalkyle, carboxy ou alcoxycarbonyle, ou R^{10} et R^{11} en combinaison représentent un groupe qui forme un cycloalkyle et l, m, et n sont chacun 0 ou un nombre entier de 1 à 3,
Rb est un atome d'hydrogène, un alkyle linéaire ou ramifié ayant de 1 à 10 atomes de carbone, un aralkyle dans lequel l'alkyle a de 1 à 4 atomes de carbone, un aminoalkyle ou un mono- ou dialkylaminoalkyle ; et
Rc est un hétérocycle éventuellement substitué contenant un atome d'azote,
un isomère optique ou cis-trans de celui-ci ou un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci.

3. Composé pour son utilisation comme dans la revendication 2, dans lequel le composé est (+)-trans-4-(1-aminoéthyl)-1-(4-pyridylcarbamoyl)-cyclohexane, (+)-trans-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoéthyl)cyclohexanecarboxamide, (R)-(+)-N-(4-pyridyl)-4-(1-aminoéthyl)benzamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoéthyl)-benzamide ou un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci.

4. Composé pour son utilisation comme dans la revendication 2 destiné à être administré à un site local dans l'oeil.

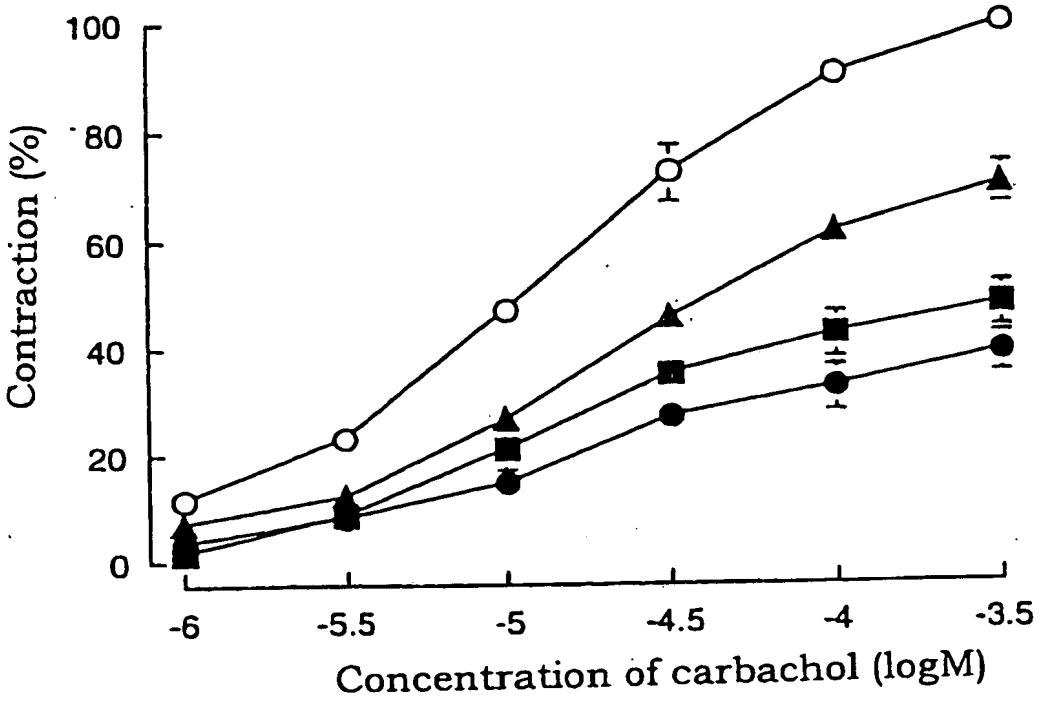
5. Composé pour son utilisation comme dans la revendication 2 destiné à être administré sous la forme d'une goutte oculaire à l'oeil.

6. Composé pour son utilisation comme dans la revendication 2, dans lequel le composé est (R)-(+)-N-(1H-pyrrolo [2,3-b]pyridin-4-yl)-4-(1-aminoéthyl)-benzamide ou un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci.

7. Composé pour son utilisation comme dans la revendication 2, dans lequel le composé est un sel d'acide chlorhydrique de (R)-(+)-N-(1H-pyrrolo[2,3-b]-pyridin-4-yl)-4-(1-aminoéthyl)-benzamide.

8. Agent comprenant le composé selon l'une quelconque des revendications 1 à 7 pour son utilisation pour prévenir et traiter l'asthénopie ou la pseudo-myopie.

FIG. 1


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

REFERENCES CITED IN THE DESCRIPTION

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