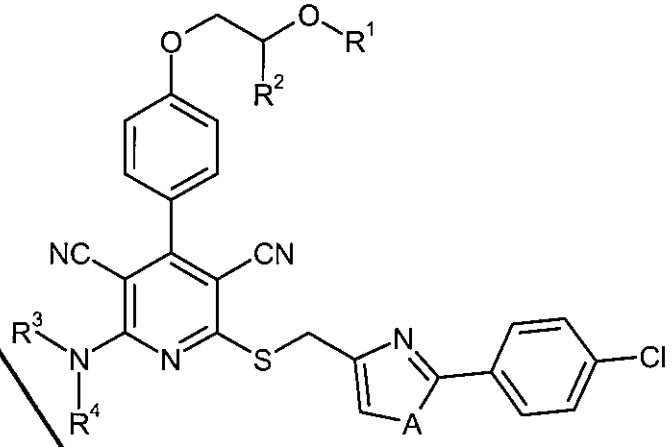
Claims

1. Compound of formula (I)

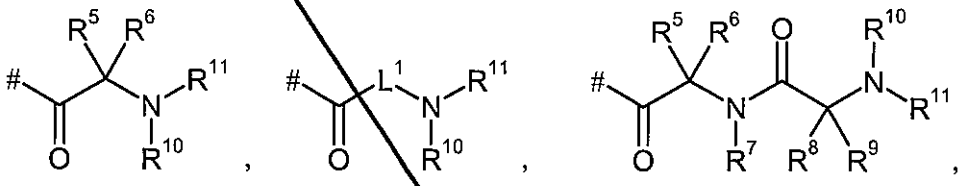


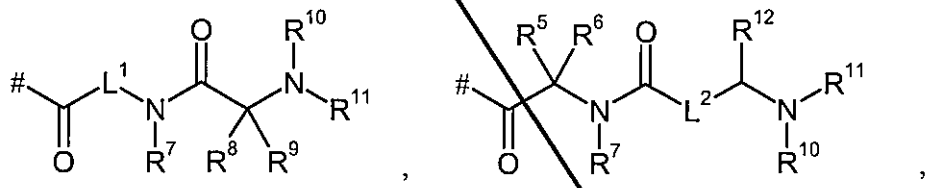
(I),

in which

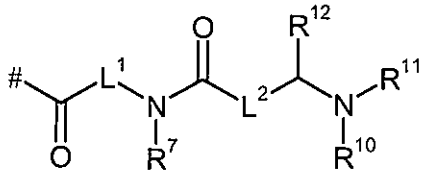
A is oxygen or sulfur,

R^1 is hydrogen or a group of the formula





or



in which

is the attachment to the oxygen-atom,

L^1 is linear (C_2-C_4)-alkanediyl,

L^2 is linear (C_1-C_3)-alkanediyl,

R^5 and R^8 are identical or different and independently selected from the group consisting of hydrogen or a side group of a natural α-amino acid or its homologues or isomers,

R^6 and R^9 are independently selected from hydrogen or methyl,

R^7 is hydrogen or (C_1-C_4)-alkyl,

or

R^7 and R^9 form together with the atoms which they are attached to a pyrrolidine- or piperidine-ring,

R^{10} and R^{11} are identical or different and are indenpentdently selected from hydrogen or (C_1-C_4)-alkyl,

wherein (C_1-C_4)-alkyl may be substituted with one group selected from hydroxy, (C_1-C_4)-alkoxy, amino, mono-(C_1-C_4)-alkylamino or di-(C_1-C_4)-alkylamino,

or

R^{10} and R^8 form together with the atoms which they are attached to a pyrrolidine- or piperidine-ring,

and

R^{12} is hydrogen or hydroxycarbonyl,

R^2 is hydrogen or a group of the formula $-CH_2OR^1$,

wherein R^1 is defined as above,

R^3 is hydrogen, methyl or ethyl,

R^4 is hydrogen, methyl or ethyl,

or

R^3 and R^4 form together with the nitrogen-atom, which they are bound to, a azetidine-, pyrrolidine- or piperidine-ring,

wherein the azetidine-, pyrrolidine- or piperidine-ring may be substituted with one or 2 substituents independently selected from the group fluoro, trifluoromethyl, methyl, ethyl, methoxy and ethoxy,

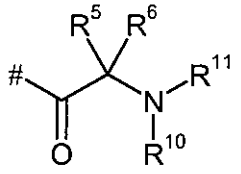
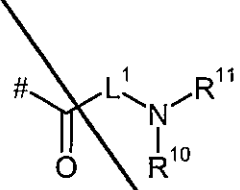
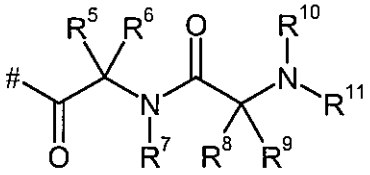
or their salts, solvates and solvates of the salts

for use in the treatment and/or prophylaxis of glaucoma, normotensive glaucoma, ocular hypertension and/or combinations thereof.

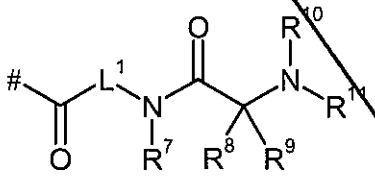
2. Compound of formula (I) according to claim 1 wherein

A is sulfur,

R^1 is a group of the formula


,

,


or



in which

is the attachment to the oxygen-atom,

L^1 is ethane-1,2-diyl,

R^5 is hydrogen, methyl, propane-2-yl, 1-methylpropane-1-yl, 2-methyl-propane-1-yl, hydroxymethyl or 1-hydroxymethyl,

R^6 is hydrogen,

R^7 is hydrogen,

R^8 is hydrogen, methyl, propan-2-yl, 1-methylpropan-1-yl, 2-methylpropan-1-yl, imidazol-4-ylmethyl, hydroxymethyl, hydroxyethyl, 2-carboxyethyl, 4-aminobutan-1-yl or 2-aminoethyl,

R^9 is hydrogen,

R^{10} is hydrogen,

R^{11} is hydrogen,

or

R^{10} and R^8 form together with the atoms which they are attached to a pyrrolidine -ring,

R^2 is hydrogen

R^3 is hydrogen,

R^4 is hydrogen,

or

R^3 and R^4 form together with the nitrogen-atom, which they are bound to, a azetidine-, pyrrolidine- or piperidine-ring,

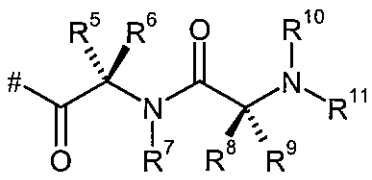
and its salts, solvates and solvates of the salts,

for use in the treatment and/or prophylaxis of glaucoma, normotensive glaucoma, ocular hypertension and/or combinations thereof.

3. Compound of formula (I) according to claim 1 wherein

A is sulfur,

R^1 is a group of the formula



,

in which

is the attachment to the oxygen-atom,

R^5 is hydrogen, methyl, propan-2-yl, 2-methylpropan-1-yl, benzyl, hydroxymethyl or 1-hydroxyethyl,

R^6 is hydrogen,

R^7 is hydrogen,

R^8 is hydrogen, methyl, propan-2-yl, 1-methylpropan-1-yl, 2-methylpropan-1-yl, imidazol-4-ylmethyl, 4-aminobutan-1-yl, 2-aminoethyl, 3-aminopropan-1-yl, aminomethyl or 3-guanidinopropan-1-yl,

R^9 is hydrogen,

R^{10} is hydrogen,

R^{11} is hydrogen,

R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

and its salts, solvates and solvates of the salts,

for use in the treatment and/or prophylaxis of glaucoma, normotensive glaucoma, ocular hypertension and/or combinations thereof.

4. Compound of formula (I) according to any of claims 1 to 3 selected from:

2-{4-[2-Amino-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]phenoxy}ethyl-L-lysyl-D-alaninate-Dihydrochloride,

2-{4-[2-Amino-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]phenoxy}ethyl-L-arginyl-D-alaninate-Dihydrochloride,

2-{4-[2-Amino-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]phenoxy}ethyl-L-lysyl-D-valinate-Dihydrochloride,

2-{4-[2-Amino-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]phenoxy}ethyl-L-arginyl-D-valinate- Trihydrochloride,

2-{4-[2-Amino-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]phenoxy}ethyl-L-lysyl-D-phenylalaninate-Dihydrochloride,

2-{4-[2-(Azetidin-1-yl)-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]phenoxy}ethyl-beta-alaninate-Trifluoroacetate,

2-{4-[2-(Azetidin-1-yl)-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]phenoxy}ethyl-L-ornithinate-Bis(trifluoroacetate),

2-{4-[2-(Azetidin-1-yl)-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]phenoxy}ethyl-L-lysyl-L-alaninate-Bis(trifluoroacetate),

2-{4-[2-({[2-(4-Chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyano-6-(pyrrolidin-1-yl)pyridin-4-yl]phenoxy}ethyl-L-alanyl-L-alaninate-Hydrochloride,

2-{4-[2-({[2-(4-Chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyano-6-(pyrrolidin-1-yl)pyridin-4-yl]phenoxy}ethyl-L-isoleucyl-L-alaninate-Hydrochloride,

2-{4-[2-({[2-(4-Chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyano-6-(pyrrolidin-1-yl)pyridin-4-yl]phenoxy}ethyl-glycyl-L-leucinate-Hydrochloride,

(2*S*)-3-{4-[2-Amino-6-({[2-(4-chlorophenyl)-1,3-oxazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]phenoxy}propan-1,2-diyl-(2*S*,2'*S*)-bis(2-{[(2*S*)-2-aminopropanoyl]amino}propanoate)-Dihydrochloride

or their salts, solvates and solvates of the salts,

for use in the treatment and/or prophylaxis of glaucoma, normotensive glaucoma, ocular hypertension and/or combinations thereof.

5. The use according to any of claims 1 to 4, wherein the compound is administered topically to the eye.

6. An ophthalmic composition comprising a compound of formula (I) as defined in any of claims 1 to 4 and a pharmaceutically acceptable vehicle or excipient.

7. The use according to any of claims 1 to 4, wherein compound of formula one is administered topically in combination with at least one further active compound selected from the group consisting of alpha adrenergic agonists, beta blockers and carbonic anhydrase inhibitors.

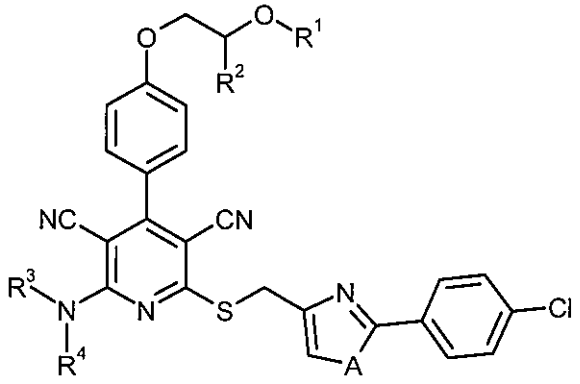
8. The use of a compound according to any of claims 1 to 4 in combination with a inert, non-toxic, pharmaceutically acceptable additive in the manufacture of a medicament for the treatment and/or prophylaxis of glaucoma and ocular hypertension.

9. The use according to claim 8 wherein the medicament further comprises at least one further active compound selected from the group consisting of alpha adrenergic agonists, beta blockers and carbonic anhydrase inhibitors.

10. A medicament, comprising a compound of the formula (I) as defined in any of claims 1 to 4 in combination with one or more further active ingredients selected from the group consisting of alpha adrenergic agonist, beta blocker and carbonic anhydrase inhibitor.

Claims

1. The use of a compound of formula (I)

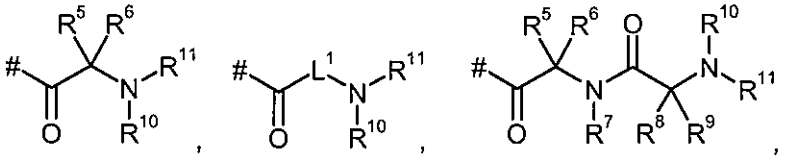


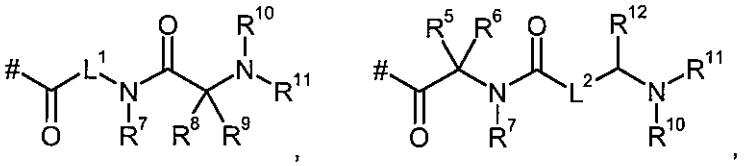
(I),

in which

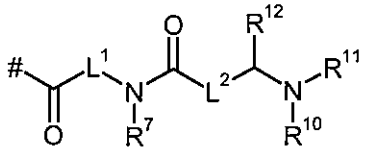
A is oxygen or sulfur,

R^1 is hydrogen or a group of the formula





or



in which

\# is the attachment to the oxygen-atom,

L^1 is linear (C_2-C_4)-alkanediyl,

L^2 is linear (C_1-C_3)-alkanediyl,

R^5 and R^8 are identical or different and independently selected from the group consisting of hydrogen or a side group of a natural α-amino acid or its homologues or isomers,

R^6 and R^9 are independently selected from hydrogen or methyl,

R^7 is hydrogen or (C_1-C_4)-alkyl,

or

R^7 and R^5 form together with the atoms which they are attached to a pyrrolidine- or piperidine-ring,

R^{10} and R^{11} are identical or different and are indenpentdently selected from hydrogen or (C_1-C_4)-alkyl,

wherein (C_1-C_4)-alkyl may be substituted with one group selected from hydroxy, (C_1-C_4)-alkoxy, amino, mono-(C_1-C_4)-alkylamino or di-(C_1-C_4)-alkylamino,

or

R^{10} and R^8 form together with the atoms which they are attached to a pyrrolidine- or piperidine-ring,

and

R^{12} is hydrogen or hydroxycarbonyl,

R^2 is hydrogen or a group of the formula $-CH_2OR^1$,

wherein R^1 is defined as above,

R^3 is hydrogen, methyl or ethyl,

R^4 is hydrogen, methyl or ethyl,

or

R^3 and R^4 form together with the nitrogen-atom, which they are bound to, a azetidine-, pyrrolidine- or piperidine-ring,

wherein the azetidine-, pyrrolidine- or piperidine-ring may be substituted with one or 2 substituents independently selected from the group fluoro, trifluoromethyl, methyl, ethyl, methoxy and ethoxy,

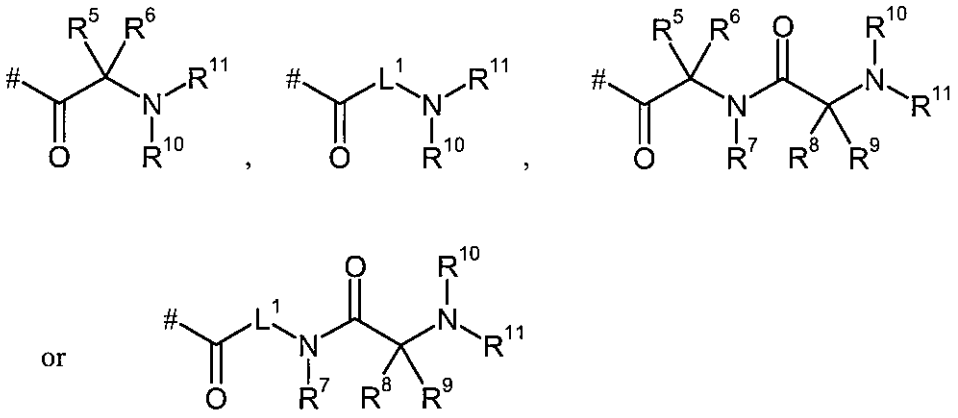
or their salts, solvates and solvates of the salts

in the manufacture of a medicament for the treatment and/or prophylaxis of glaucoma, normotensive glaucoma, ocular hypertension and/or combinations thereof.

2. The use of a compound of formula (I) according to claim 1 wherein

A is sulfur,

R^1 is a group of the formula



in which

is the attachment to the oxygen-atom,

L^1 is ethane-1,2-diyl,

R^5 is hydrogen, methyl, propane-2-yl, 1-methylpropane-1-yl, 2-methylpropane-1-yl, hydroxymethyl or 1-hydroxymethyl,

R^6 is hydrogen,

R^7 is hydrogen,

R^8 is hydrogen, methyl, propan-2-yl, 1-methylpropan-1-yl, 2-methylpropan-1-yl, imidazol-4-ylmethyl, hydroxymethyl, hydroxyethyl, 2-carboxyethyl, 4-aminobutan-1-yl or 2-aminoethyl,

R^9 is hydrogen,

R^{10} is hydrogen,

R^{11} is hydrogen,

or

R^{10} and R^8 form together with the atoms which they are attached to a pyrrolidine -ring,

R^2 is hydrogen

R^3 is hydrogen,

R^4 is hydrogen,

or

R^3 and R^4 form together with the nitrogen-atom, which they are bound to, a azetidine-, pyrrolidine- or piperidine-ring,

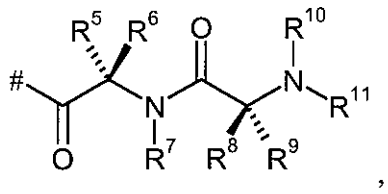
and its salts, solvates and solvates of the salts,

in the manufacture of a medicament for the treatment and/or prophylaxis of glaucoma, normotensive glaucoma, ocular hypertension and/or combinations thereof.

3. The use of a compound of formula (I) according to claim 1 wherein

A is sulfur,

R^1 is a group of the formula



,

in which

is the attachment to the oxygen-atom,

R^5 is hydrogen, methyl, propan-2-yl, 2-methylpropan-1-yl, benzyl, hydroxymethyl or 1-hydroxyethyl,

R^6 is hydrogen,

R^7 is hydrogen,

R^8 is hydrogen, methyl, propan-2-yl, 1-methylpropan-1-yl, 2-methylpropan-1-yl, imidazol-4-ylmethyl, 4-aminobutan-1-yl, 2-aminoethyl, 3-aminopropan-1-yl, aminomethyl or 3-guanidinopropan-1-yl,

R^9 is hydrogen,

R^{10} is hydrogen,

R^{11} is hydrogen,

R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

and its salts, solvates and solvates of the salts,

in the manufacture of a medicament for the treatment and/or prophylaxis of glaucoma, normotensive glaucoma, ocular hypertension and/or combinations thereof.

4. The use of a compound of formula (I) according to any of claims 1 to 3 selected from:

2-{4-[2-Amino-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]-phenoxy}ethyl-L-lysyl-D-alaninate-Dihydrochloride,

2-{4-[2-Amino-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]-phenoxy}ethyl-L-arginyl-D-alaninate-Dihydrochloride,

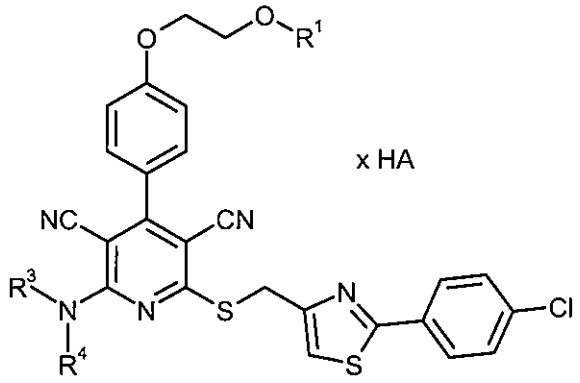
2-{4-[2-Amino-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]-phenoxy}ethyl-L-lysyl-D-valinate-Dihydrochloride,

2-{4-[2-Amino-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]-phenoxy}ethyl-L-arginyl-D-valinate- Trihydrochloride,

2-{4-[2-Amino-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]-phenoxy}ethyl-L-lysyl-D-phenylalaninate-Dihydrochloride,

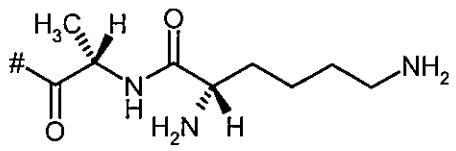
2-{4-[2-(Azetidin-1-yl)-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]phenoxy}ethyl-beta-alaninate-Trifluoroacetate,
2-{4-[2-(Azetidin-1-yl)-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]phenoxy}ethyl-L-ornithinate-Bis(trifluoroacetate),
2-{4-[2-(Azetidin-1-yl)-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]phenoxy}ethyl-L-lysyl-L-alaninate-Bis(trifluoroacetate),
2-{4-[2-({[2-(4-Chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyano-6-(pyrrolidin-1-yl)pyridin-4-yl]phenoxy}ethyl-L-alanyl-L-alaninate-Hydrochloride,
2-{4-[2-({[2-(4-Chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyano-6-(pyrrolidin-1-yl)pyridin-4-yl]phenoxy}ethyl-L-isoleucyl-L-alaninate-Hydrochloride,
2-{4-[2-({[2-(4-Chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyano-6-(pyrrolidin-1-yl)pyridin-4-yl]phenoxy}ethyl-glycyl-L-leucinate-Hydrochloride,
(2*S*)-3-{4-[2-Amino-6-({[2-(4-chlorophenyl)-1,3-oxazol-4-yl]methyl}sulfanyl)-3,5-dicyanopyridin-4-yl]phenoxy}propan-1,2-diyl-(2*S*,2'*S*)-bis(2-{[(2*S*)-2-aminopropanoyl]amino}propanoate)-Dihydrochloride
or their salts, solvates and solvates of the salts,
in the manufacture of a medicament for the treatment and/or prophylaxis of glaucoma, normotensive glaucoma, ocular hypertension and/or combinations thereof.

5. The use of a compound of formula (I) according to claim 1 having the formula:



wherein

R^1 is



R^3 is hydrogen,

R^4 is hydrogen,

HA is 2 HCl,

in the manufacture of a medicament for the treatment and/or prophylaxis of glaucoma, normotensive glaucoma, ocular hypertension and/or combinations thereof.

6. The use according to any of claims 1 to 5, wherein the compound is administered topically to the eye.

7. The use according to any of claims 1 to 6 wherein the medicament further comprises at least one further active compound selected from the group consisting of alpha adrenergic agonists, beta blockers and carbonic anhydrase inhibitors.

8. The use of a compound of formula (I) according to any of claims 1 to 5 in a method for the treatment and/or prophylaxis of glaucoma, normotensive glaucoma, ocular hypertension and/or combinations thereof without effecting hemodynamics.

9. The use according to Claim 8 without effecting the blood pressure.

10. The use according to Claim 8 without effecting the heart rate.