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(54) **Title:** NEUTRAL ENDOPEPTIDASE (NEP) AND HUMAN SOLUBLE ENDOPEPTIDASE (HSEP) INHIBITORS FOR PROPHYLAXIS AND TREATMENT OF EYE DISEASES

(57) **Abstract:** The invention relates to a novel use of benzazepine, benzoxazepine, benzothiazepine-N- acetic acid and phosphono-substituted benzazepinone derivatives having both neutral endopeptidase (NEP) and/or human soluble endopeptidase (hSEP), and endothelin convertase (ECE) inhibitory activity. The compounds of the invention are useful for the preparation of pharmaceutical compositions for prophylaxis and treatment of eye diseases.

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AMENDED CLAIMS
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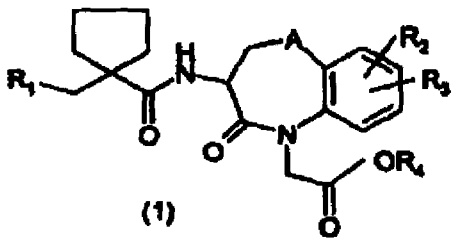
NEUTRAL ENDOPEPTIDASE (NEP) AND HUMAN SOLUBLE ENDOPEPTIDASE (hSEP) INHIBITORS FOR PROPHYLAXIS AND TREATMENT OF EYE DISEASES

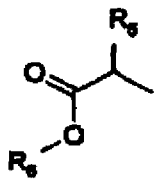
CLAIMS (Amendment under Art. 19 PCT – clean version)

1. Compounds of the general formula (1) wherein:

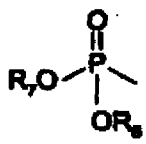


(1)

R1 stands for a group with formula (2) or (3):



(2)



(3)

A represents CH2, O or S,

R2 and R3 independently represent hydrogen or halogen,

R4 and R6 independently represent hydrogen or a biolabile carboxylic ester forming group;

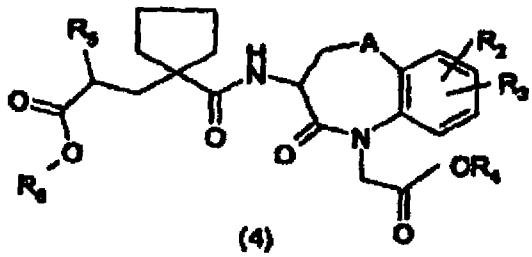
R5 is selected from the group consisting of (C1-C6)alkoxy(C1-C6)alkyl which may be substituted by a (C1-C6) alkoxy, phenyl-(C1-C6)-alkyl and phenyloxy-(C1-C6)-alkyl wherein the phenyl group may be substituted with (C1-C6)alkyl, (C1-C6)-alkoxy or halogen, and naphtyl-(C1-C6)-alkyl,

R7 and R8 independently represent hydrogen or a group forming a biolabile phosphonic acid ester,

all stereoisomers, as well as pharmaceutically acceptable salts thereof, for use in the prophylaxis and/or treatment and/or for use in the preparation of pharmaceutical compositions for prophylaxis and/or treatment of optic and/or eye diseases selected from the group consisting of such diseases as e.g. (i) all forms of primary and secondary glaucoma, preferably such as e.g.

primary open-angle glaucoma, normal-tension glaucoma, primary angle-closure glaucoma, pseudoexfoliation syndrome and glaucoma, pigment dispersion syndrome and glaucoma, neovascular glaucoma, inflammatory glaucoma, lens-related glaucoma, traumatic glaucoma, primary congenital glaucoma, iatrogenic induced glaucoma, and malignant glaucoma; (ii) aquired macular disorders, preferably such as e.g. age-related macular degeneration, idiopathic choroidal neovascularisation, central serous chorioretinopathy, vitreomacular interface disorders, idiopathic macular telangiectasia, cystoid macular oedema, and microcystic macular oedema; (iii) optic neuropathy, preferably such as e.g. anterior or posterior ischemic optic neuropathy; (iv) optic neuritis; (v) uveitis, preferably such as e.g. anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis; (vi) hereditary fundus dystrophies, preferably such as e.g. cone dystrophy, cone-rod dystrophy, rod dystrophy, Stargardt's disease, Bietti's crystalline corneoretinal dystrophy, familial benign fleck retina, Best vitelliform macular dystrophy, adult-onset vitelliform macular dystrophy, North Carolina macular dystrophy, familial dominant drusen, and concentric annular macular dystrophy; (vii) retinal vascular diseases, preferably such as e.g. diabetic retinopathy, non-diabetic retinopathy, retinal venous occlusive disease, retinal arterial occlusive disease, ocular ischemic syndrome, hypertensive eye disease, sickle cell retinopathy, thalassemia retinopathy, retinopathy of prematurity, retinal artery macroaneurysm, primary retinal telangiectasia, Eales disease, and radiation retinopathy; (viii) scleritis and episcleritis; (ix) retinal detachments; (x) trauma to the eye globe; (xi) vitreous opacities, preferably such as e.g. vitreous hemorrhage, and asteroid hyalosis; (xii) myopia and degenerative myopia; (xiii) postsurgical trauma, preferably such as e.g. mechanical trauma due to conventional surgery, thermotrauma due to laser surgery, and trauma induced by cryosurgery; (xiv) dry eye disease; (xv) corneal disorders, preferably such as abrasions, lacerations, ulcerations, dystrophies, opacities, endothelial and epithelial decompensation, post-surgical oedema, corneal degenerations, corneal vascularisation; and corneal ectasias, preferably such as keratoconus, with the proviso that said pharmaceutical compositions do not contain an aldosterone receptor antagonist.

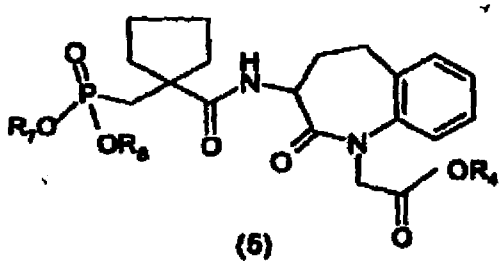
2. A compound of the general formula (4):



(4)

wherein the symbols have the meanings as given in claim 1, all stereoisomers, as well as pharmaceutically acceptable salts thereof, for use in the prophylaxis and/or treatment and/or for use in the preparation of pharmaceutical compositions for prophylaxis and/or treatment of optic and/or eye diseases as claimed in claim 1.

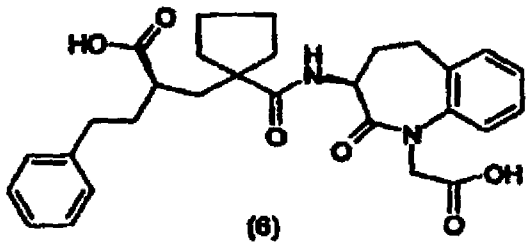
3. A compound of the general formula (5):



(5)

wherein the symbols have the meanings as given in claim 1, all stereoisomers, as well as pharmaceutically acceptable salts thereof, for use in the prophylaxis and/or treatment and/or for use in the preparation of pharmaceutical compositions for prophylaxis and/or treatment of optic and/or eye diseases as claimed in claim 1.

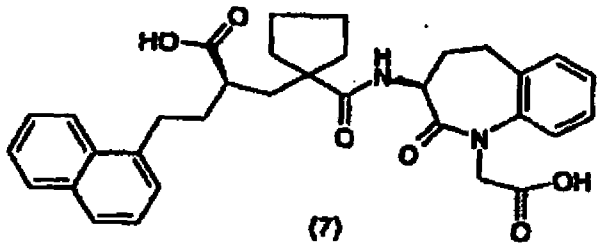
4. Compound (2R)-2-{[1-({[(3S)-1-(carboxymethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-3-yl]amino}carbonyl)cyclopent-yl]methyl}-4-phenylbutanoic acid having formula (6):



(6)

as well as pharmaceutically acceptable salts thereof, for use in the prophylaxis and/or treatment for use in the preparation of pharmaceutical compositions for prophylaxis and/or treatment of optic and/or eye diseases as claimed in claim 1.

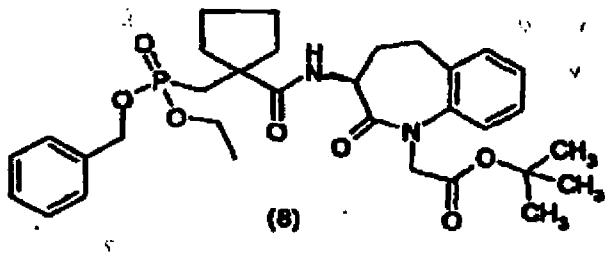
5. Compound (2R)-2-{(1-({[(3S)-1-(carboxymethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-3-yl]amino}carbonyl)cyclopent-yl]methyl}-4-(1-naphthyl)butanoic acid having formula (7):



(7)

as well as pharmaceutically acceptable salts thereof, for use in the prophylaxis and/or treatment and/or for use in the preparation of pharmaceutical compositions for prophylaxis and/or treatment of optic and/or eye diseases as claimed in claim 1.

6. Compound tert-butyl-((3S)-3-{[(1-{[(benzyloxy)(ethoxy)phosphoryl]methyl}cyclopentyl)-carbonyl]amino)-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)acetate having formula (8):



(8)

as well as pharmaceutically acceptable salts thereof, for use in the prophylaxis and/or treatment and/or for use in the preparation of pharmaceutical compositions for prophylaxis and/or treatment of optic and/or eye diseases as claimed in claim 1.

7. Use as claimed in any of the claims 1-6, characterized in that the pharmaceutically acceptable salt is selected from the group consisting of the lithium salt, the calcium salt, the magnesium salt and the zinc salt, and that the pharmaceutically acceptable salt preferably is the calcium salt.

8. Use as claimed in any of the claims 1-6, characterized in that said prophylaxis and/or treatment is for all forms of primary and secondary glaucoma, preferably such as e.g. primary open-angle glaucoma, normal-tension glaucoma, primary angle-closure glaucoma, pseudoexfoliation syndrome and glaucoma, pigment dispersion syndrome and glaucoma, neovascular glaucoma, inflammatory glaucoma, lens-related glaucoma, traumatic glaucoma, primary congenital glaucoma, iatrogenic induced glaucoma, or malignant glaucoma.

9. Use as claimed in any of the claims 1-6, characterized in that said prophylaxis and/or treatment is for aquired macular disorders, preferably such as e.g. age-related macular degeneration, idiopathic choroidal neovascularisation, central serous chorioretinopathy, vitreomacular interface disorders, idiopathic macular telangiectasia, cystoid macular oedema, or microcystic macular oedema.

10. Use as claimed in any of the claims 1-6, characterized in that said prophylaxis and/or treatment is for optic neuropathy, preferably such as e.g. anterior or posterior ischemic optic neuropathy; or is for scleritis or episcleritis; or is for optic neuritis; or is for uveitis, preferably such as e.g. anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis.

11. Use as claimed in any of the claims 1-6, characterized in that said prophylaxis and/or treatment is for hereditary fundus dystrophies, preferably such as e.g. cone dystrophy, cone-rod dystrophy, rod dystrophy, Stargardt's disease, Bietti's crystalline corneoretinal dystrophy, familial benign fleck retina, Best vitelliform macular dystrophy, adult-onset vitelliform macular dystrophy, North Carolina macular dystrophy, familial dominant drusen, or concentric annular macular dystrophy.

12. Use as claimed in any of the claims 1-6, characterized in that said prophylaxis and/or treatment is for retinal vascular diseases, preferably such as e.g. diabetic retinopathy, non-diabetic retinopathy, retinal venous occlusive disease, retinal arterial occlusive disease, ocular ischemic syndrome, hypertensive eye disease, sickle cell retinopathy, thalassemia retinopathy, retinopathy of prematurity, retinal artery macroaneurysm, primary retinal telangiectasia, Eales disease, or radiation retinopathy.

13. Use as claimed in any of the claims 1-6, characterized in that said prophylaxis and/or treatment is for myopia, or degenerative myopia; or is for dry eye disease.

14. Use as claimed in any of the claims 1-6, characterized in that said treatment is for trauma to the eye globe; or is for postsurgical trauma, preferably such as e.g. mechanical trauma due to conventional surgery, thermotrauma due to laser surgery, or trauma induced by cryosurgery; or is for vitreous opacities, preferably such as e.g. vitreous haemorrhage, or asteroid hyalosis; or is for retinal detachments.

15. Use as claimed in any of the claims 1-6, characterized in that said prophylaxis and/or treatment is for corneal disorders, preferably such as abrasions, lacerations, ulcerations, dystrophies, opacities, endothelial and epithelial decompensation, post-surgical oedema, corneal degenerations, or corneal vascularisation; or is for corneal ectasias, preferably such as keratoconus.