vision is needed for seeing objects clearly and for common daily tasks such as reading and driving. AMD affects the macula, the central part the retina that allows the eye to see fine details. There are two forms of AMD—wet and dry.

Dry AMD is when the macula thins overtime as part of aging process, gradually blurring central vision. The dry form is more common and accounts for 70–90% of cases of AMD and it progresses more slowly than the wet form. Over time, as less of the macula functions, central vision is gradually lost in the affected eye. Dry AMD generally affects both eyes. One of the most common early signs of dry AMD is drusen.

The exudative ("wet"), or neovascular form of AMD - wet AMD - causes vision loss due to abnormal blood vessel growth (choroidal neovascularization) in the choriocapillaris, through Bruch's membrane, ultimately leading to blood and protein leakage below the macula. Bleeding, leaking, and scarring from these blood vessels may lead to detachment of the retinal pigment epithelium and irreversible damage to the photoreceptors and rapid vision loss if left untreated.

Summary

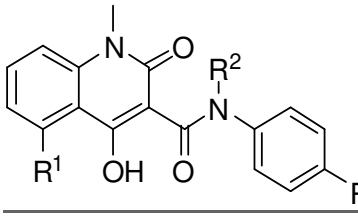
As described above, a treatment for an eye disease or eye disorder associated with excessive vascularisation such as wet age-related macular degeneration is highly desired. Such a treatment could potentially prevent or reduce damage to eye tissues, such as the macula, which would severely improve the prognosis for subjects suffering from such eye diseases or eye disorders.

The present disclosure relates to a composition comprising a compound of formula (I) for use in the treatment of an eye disease or eye disorder associated with excessive vascularisation of the eye. The inventors of the present disclosure have surprisingly found that treatment of induced vascularisation of eye tissues resulted in reduced vascularisation of either cornea or choroid. More specifically, the inventors have surprisingly found that compositions comprising compounds of the ~~invention~~disclosure suppress choroidal neovascularisation in a laser-induced choroidal neovascularisation rat model. The inventors have also found a surprising effect in the treatment growth-factor-stimulated neovascularisation in a mouse model, where compositions comprising compounds of the ~~invention~~disclosure were capable of reducing the area of vascularisation. These findings enable a complete new way to address the treatment of diseases and disorders associated with excessive vascularisation of the eye, which could potentially lead to better prognosis for patients sufferings from diseases such as corneal

neovascularisation, neovascularisation of the iris, neovascularisation of the ciliary body, corneal pannus, choroidal neovascularisation, retinal neovascularisation, wet age-related macular degeneration, proliferative diabetic retinopathy, retinopathy of prematurity, and ischemic retinopathy.

The present disclosure thus provides a composition comprising a compound according to any one of formulas (I) to (IX) for use in treatment of an eye disease or eye disorder.

In one aspect, the present disclosure refers to a use a composition comprising a compound according to formula (I):



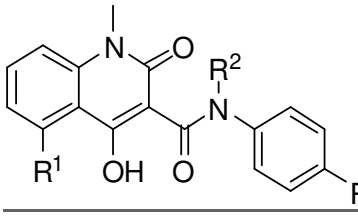
formula (I),

wherein:

R1 is chloro, R2 is ethyl or hydrogen, and R3 is hydrogen,

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of an eye disease or eye disorder selected from the group consisting of corneal neovascularisation, neovascularisation of the iris, neovascularisation of the ciliary body, corneal pannus, choroidal neovascularisation, retinal neovascularisation, wet age-related macular degeneration, proliferative diabetic retinopathy, retinopathy of prematurity, and ischemic retinopathy.

In another aspect, the present disclosure refers to a use of a composition comprising a compound according to formula (I):



formula (I),

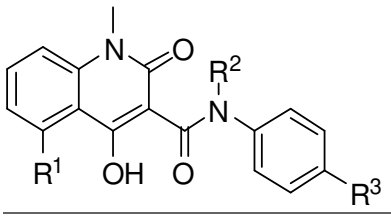
wherein:

R^1 is chloro, R^2 is ethyl or hydrogen, and R^3 is hydrogen,

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combinatorial therapy for treating an eye disease or eye disorder selected from

the group consisting of corneal neovascularisation, neovascularisation of the iris, neovascularisation of the ciliary body, corneal pannus, choroidal neovascularisation, retinal neovascularisation, wet age-related macular degeneration, proliferative diabetic retinopathy, retinopathy of prematurity, and ischemic retinopathy,
wherein said medicament is to be administered in combination with an angiogenesis inhibitor or a VEGF inhibitor.

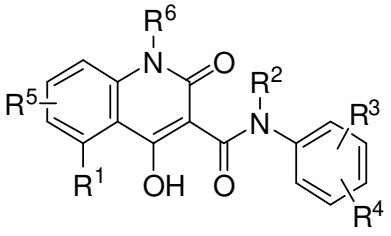
In another aspect, the present disclosure refers to a use of a composition comprising a compound according to formula (I):



formula (I),

wherein:
R1 is chloro, R2 is ethyl or hydrogen, and R3 is hydrogen,
or a pharmaceutically acceptable salt thereof, in the manufacture of a first medicament, and
use of an angiogenesis inhibitor or a VEGF inhibitor in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat an eye disease or eye disorder selected from the group consisting of corneal neovascularisation, neovascularisation of the iris, neovascularisation of the ciliary body, corneal pannus, choroidal neovascularisation, retinal neovascularisation, wet age-related macular degeneration, proliferative diabetic retinopathy, retinopathy of prematurity, and ischemic retinopathy.

One ~~aspect~~example of the disclosure provides for a composition comprising a compound according to formula (IX):

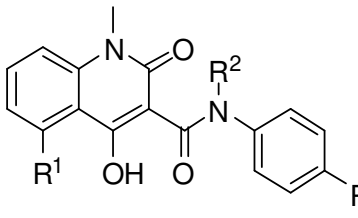


formula (IX)

wherein

R^1 is selected from the group consisting of hydrogen, hydroxy, methyl, ethyl, n-propyl, iso-propyl, methoxy, ethoxy, fluoro, chloro, bromo, trifluoromethyl, and trifluoromethoxy,
R^2 is selected from the group consisting of hydrogen and C1-C4 alkyl, such as methyl, ethyl, or vinyl,
R^3 is selected from the group consisting of hydrogen, hydroxy, methyl, methoxy, fluoro, chloro, bromo, trifluoromethyl, and trifluoromethoxy,
R^4 is selected from the group consisting of hydrogen, fluoro and chloro, with the proviso that R^4 is selected from fluoro and chloro only when R^3 is selected from fluoro and chloro,
R^5 is hydrogen or hydroxy, and
R^6 is methyl or hydrogen,
or a pharmaceutically acceptable salt thereof, for use in the treatment of an eye disease or eye disorder.

In one ~~aspect~~example, a composition comprising a compound of formula (I) is provided:


formula (I),

wherein:

R^1 is chloro, R^2 is ethyl, and R^3 is hydrogen,

R^1 is methoxy, R^2 is methyl, and R^3 is trifluoromethyl,

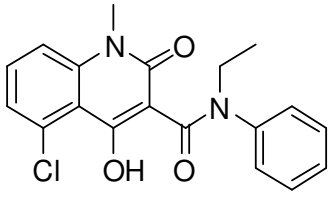
R^1 is chloro, R^2 is hydrogen, and R^3 is hydrogen,

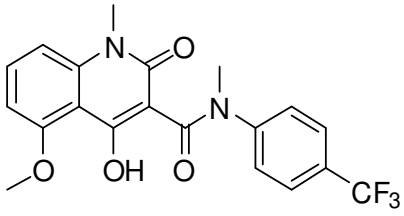
or

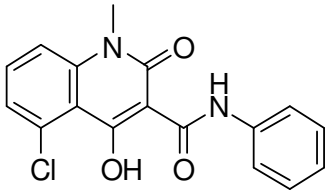
R^1 is methoxy, R^2 is hydrogen, and R^3 is trifluoromethyl;

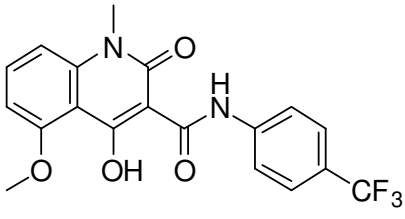
or a pharmaceutically acceptable salt thereof, for use in the treatment of an eye disease or eye disorder.

One specific ~~aspect~~example of the disclosure provides for a composition comprising a compound of formula (II), formula (III), formula (IV), or formula (V) is provided:


formula (II),


formula (III),


formula (IV),

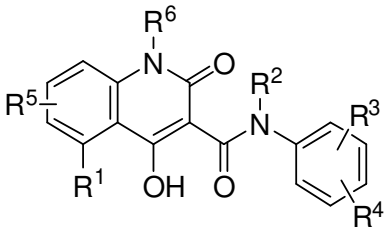

formula (V),

or a pharmaceutically acceptable salt thereof, for use in the treatment of an eye disease or eye disorder.

A specific ~~aspect~~example of the present disclosure provides for a composition comprising a compound selected from the group consisting of:
laquinimod,
5-chloro-N-ethyl-4-hydroxy-N-(4-hydroxyphenyl)-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxamide,
5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-1,2-dihydroquinoline-3-carboxamide,
5-chloro-N-ethyl-4-hydroxy-2-oxo-N-phenyl-1,2-dihydroquinoline-3-carboxamide,
5-chloro-N-ethyl-4,8-dihydroxy-1-methyl-2-oxo-N-phenyl-1,2-dihydroquinoline-3-carboxamide,
5-chloro-N-ethyl-4,7-dihydroxy-1-methyl-2-oxo-N-phenyl-1,2-dihydroquinoline-3-carboxamide,
5-chloro-N-ethyl-4,6-dihydroxy-1-methyl-2-oxo-N-phenyl-1,2-dihydroquinoline-3-carboxamide,
5-chloro-4-hydroxy-1-methyl-2-oxo-N-phenyl-N-vinyl-1,2-dihydroquinoline-3-carboxamide,
5-chloro-N-ethyl-4-hydroxy-N-(4-hydroxyphenyl)-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxamide,
N-ethyl-4-hydroxy-1-methyl-2-oxo-N-phenyl-1,2-dihydroquinoline-3-carboxamide,
5'-chloro-1-ethyl-1'-methyl-2'H-spiro[indoline-3,3'-quinoline]-2,2',4'(1'H)-trione,
tasquinimod,
4-hydroxy-5-methoxy-N-methyl-2-oxo-N-(4-(trifluoromethyl)phenyl)-1,2-dihydroquinoline-3-carboxamide,
4,5-dihydroxy-N,1-dimethyl-2-oxo-N-(4-(trifluoromethyl)phenyl)-1,2-dihydroquinoline-3-carboxamide,
4-hydroxy-5-methoxy-1-methyl-2-oxo-N-(4-(trifluoromethyl)phenyl)-1,2-dihydroquinoline-3-carboxamide,
4,6-dihydroxy-5-methoxy-N,1-dimethyl-2-oxo-N-(4-(trifluoromethyl)phenyl)-1,2-dihydroquinoline-3-carboxamide,
4,7-dihydroxy-5-methoxy-N,1-dimethyl-2-oxo-N-(4-(trifluoromethyl)phenyl)-1,2-dihydroquinoline-3-carboxamide, and

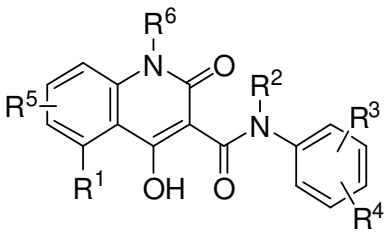
4,8-dihydroxy-5-methoxy-N,1-dimethyl-2-oxo-N-(4-(trifluoromethyl)phenyl)-1,2-dihydroquinoline-3-carboxamide,
or a pharmaceutically acceptable salt thereof, for use in the treatment of an eye disease or eye disorder.

One ~~aspect~~example of the disclosure provides for a method of treating an eye disease or eye disorder, wherein said method comprises administering a composition comprising a compound according to formula (IX):


formula (IX)

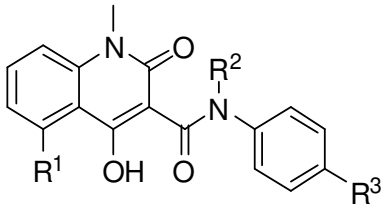
wherein
R^1 is selected from the group consisting of hydrogen, hydroxy, methyl, ethyl, n-propyl, iso-propyl, methoxy, ethoxy, fluoro, chloro, bromo, trifluoromethyl, and trifluoromethoxy,
R^2 is selected from the group consisting of hydrogen and C1-C4 alkyl, such as methyl, ethyl, or vinyl,
R^3 is selected from the group consisting of hydrogen, hydroxy, methyl, methoxy, fluoro, chloro, bromo, trifluoromethyl, and trifluoromethoxy,
R^4 is selected from the group consisting of hydrogen, fluoro and chloro, with the proviso that R^4 is selected from fluoro and chloro only when R^3 is selected from fluoro and chloro,
R^5 is hydrogen or hydroxy, and
R^6 is methyl or hydrogen,
or a pharmaceutically acceptable salt thereof.

One ~~aspect~~example of the disclosure provides for a use of a compound according to formula (IX):


formula (IX)

Claims

1. Use of a~~A~~ composition comprising a compound according to formula (I):



formula (I),

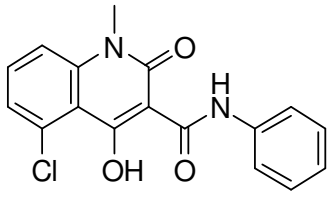
wherein:

R^1 is chloro, R^2 is ethyl or hydrogen, and R^3 is hydrogen,

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~use in~~ the treatment of an eye disease or eye disorder selected from the group consisting of corneal neovascularisation, neovascularisation of the iris, neovascularisation of the ciliary body, corneal pannus, choroidal neovascularisation, retinal neovascularisation, wet age-related macular degeneration, proliferative diabetic retinopathy, retinopathy of prematurity, and ischemic retinopathy.

2. The ~~composition for~~ use according to claim 1, wherein the compound is laquinimod, or a pharmaceutically acceptable salt thereof.

3. The ~~composition for~~ use according to claim 1, wherein the compound is a compound of formula (IV):



formula (IV),

or a pharmaceutically acceptable salt thereof.

4. The ~~composition for~~ use according to any one of the preceding claims, wherein the eye disease or eye disorder is selected from the group consisting of corneal neovascularisation, neovascularisation of the iris, neovascularisation of the ciliary body, and corneal pannus.

5. The ~~composition for~~ use according to claim 4, wherein the eye disease or eye disorder is corneal neovascularisation.

6. The ~~composition for~~ use according to any one of claims 1 to 3, wherein the eye disease or eye disorder is selected from the group consisting of proliferative diabetic retinopathy, retinopathy of prematurity, and ischemic retinopathy.

7. The ~~composition for~~ use according to claim 6, wherein the eye disease or eye disorder is proliferative diabetic retinopathy.

8. The ~~composition for~~ use according to claim 6, wherein the eye disease or eye disorder is retinopathy of prematurity.

9. The ~~composition for~~ use according to claim 6, wherein the eye disease or eye disorder is ischemic retinopathy.

10. The ~~composition for~~ use according to any one of claims 1 to 3, wherein the eye disease or eye disorder is selected from the group consisting of choroidal neovascularisation, retinal neovascularisation, and wet age-related macular degeneration.

11. The ~~composition for~~ use according to claim 10, wherein the eye disease or eye disorder is choroidal neovascularisation.

12. The ~~composition for~~ use according to claim 10, wherein the eye disease or eye disorder is retinal neovascularisation.

13. The ~~composition for~~ use according to claim 10, wherein the eye disease or eye disorder is wet age-related macular degeneration.

14. The ~~composition for~~ use according to any one of the preceding claims, wherein the composition comprises or is to be administered in combination with an angiogenesis inhibitor, such as aflibercept.

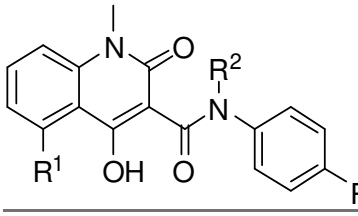
15. The ~~composition for~~ use according to any one of the preceding claims, wherein the composition comprises or is to be administered in combination with a VEGF inhibitor.

16. The ~~composition for~~ use according to claim 15, wherein the VEGF inhibitor is selected from the group consisting of aflibercept, ranibizumab, bevacizumab, brolucizumab, abicipar pegol, conbercept, and faricimab.

17. The ~~composition for~~ use according to any one of the preceding claims, wherein the composition comprises or is to be administered in combination with at least one pharmaceutically acceptable excipient.

18. The ~~composition for~~ use according to any one of the preceding claims, wherein the route of administration is topical, oral, intravitreal, subconjunctival, retrobulbar, intracameral, or systemic.

19. Use of a composition comprising a compound according to formula (I):



formula (I),

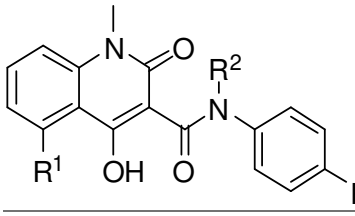
wherein:

R^1 is chloro, R^2 is ethyl or hydrogen, and R^3 is hydrogen,

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combinatorial therapy for treating an eye disease or eye disorder selected from the group consisting of corneal neovascularisation, neovascularisation of the iris, neovascularisation of the ciliary body, corneal pannus, choroidal neovascularisation, retinal neovascularisation, wet age-related macular degeneration, proliferative diabetic retinopathy, retinopathy of prematurity, and ischemic retinopathy,

wherein said medicament is to be administered in combination with an angiogenesis inhibitor or a VEGF inhibitor.

20. Use of a composition comprising a compound according to formula (I):


formula (I),

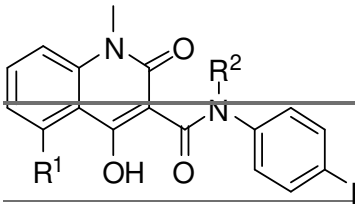
wherein:

R^1 is chloro, R^2 is ethyl or hydrogen, and R^3 is hydrogen,

or a pharmaceutically acceptable salt thereof, in the manufacture of a first medicament, and

use of an angiogenesis inhibitor or a VEGF inhibitor in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat an eye disease or eye disorder selected from the group consisting of corneal neovascularisation, neovascularisation of the iris, neovascularisation of the ciliary body, corneal pannus, choroidal neovascularisation, retinal neovascularisation, wet age-related macular degeneration, proliferative diabetic retinopathy, retinopathy of prematurity, and ischemic retinopathy.

~~19. A method of treating an eye disease or eye disorder selected from the group consisting of corneal neovascularisation, neovascularisation of the iris, neovascularisation of the ciliary body, corneal pannus, choroidal neovascularisation, retinal neovascularisation, wet age-related macular degeneration, proliferative diabetic retinopathy, retinopathy of prematurity, and ischemic retinopathy, said method comprising administering a composition comprising a therapeutically effective amount of a compound according to formula (I):~~

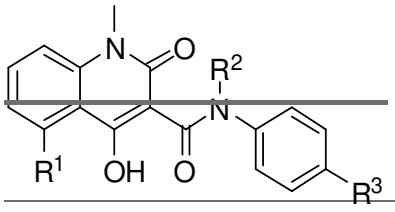

~~formula (I),~~

~~wherein:~~

~~R^1 is chloro, R^2 is ethyl or hydrogen, and R^3 is hydrogen,~~

~~or a pharmaceutically acceptable salt thereof, to a subject in need thereof.~~

~~20. Use of a compound according to formula (I):~~



formula (I),

wherein:

R^1 is chloro, R^2 is ethyl or hydrogen, and R^3 is hydrogen,

or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of an eye disease or eye disorder selected from the group consisting of corneal neovascularisation, neovascularisation of the iris, neovascularisation of the ciliary body, corneal pannus, choroidal neovascularisation, retinal neovascularisation, wet age-related macular degeneration, proliferative diabetic retinopathy, retinopathy of prematurity, and ischemic retinopathy.