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New compounds and their use as therapeutically active substances in the treatment and/or prevention of diseases involving the retinal pigment epithelium

The present invention relates to new compounds and to
5 their use as therapeutically active substances in the treatment and/or prevention of diseases involving the retinal pigment epithelium, and in particular in the treatment and/or prevention of diseases leading to atrophy, degeneration or death of the retinal pigment
10 epithelium that might also result in atrophy or loss of photoreceptors and/or retinal neovascularization.

An important family of diseases that involves degeneration and death of the retinal pigment epithelium (RPE) is macular degeneration. Macular degeneration is
15 characterized by a progressive loss of central vision associated with abnormalities of Bruch's membrane, the choroid, the neural retina and/or the retinal pigment epithelium. The macula describes the central region of the retina with an approximate diameter of 0.3 to 0.5 cm.
20 Because of its high density of cones, the macula provides detailed vision for activities such as reading, driving or recognizing faces.

So called age-related macular degeneration (AMD), the most prevalent form of macular degeneration, is associated with
25 progressive loss of visual acuity in the central portion of the visual field, changes in color vision, and abnormal dark adaptation and sensitivity. AMD is a leading cause of irreversible vision loss in the developed world affecting approximately 2% of individuals. The prevalence of AMD
30 increases with age and its etiology is multifactorial.

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Among the key contributors to the disease and its progression are the loss of functional RPE cells and changes in their basement membrane, the Bruch's membrane. The RPE is a continuous cellular monolayer lying between
5 the light-sensitive photoreceptors and the choroid, the blood supply of the retina. As the RPE cells perform a nourishing role to the highly metabolic photoreceptors by providing energy and growth factors, removing waste, and recycling essential compounds of the visual cycle, loss of
10 the RPE ultimately leads to photoreceptor failure and loss.

Two principal clinical manifestations of AMD have been described as the dry or atrophic form (hereinafter referred to as dry AMD) and the wet or neovascular form
15 (hereinafter referred to as wet AMD). Dry AMD is associated with atrophic cell death of the central retina or macula. About 10-20% of these dry AMD patients further progress to the second form, known as wet or neovascular AMD. In these advanced stages of AMD, atrophy of the RPE
20 (geographic atrophy) and/or development of new blood vessels derived from choroidal vessels (neovascularization) further result in the death of photoreceptors and central vision loss. This loss of central vision, which is crucial for reading, the
25 recognition of faces, and performing many daily tasks, essentially cuts the sufferer off from the world around.

No approved treatments currently exist for dry AMD or its advanced form known as geographic atrophy (GA), and many patients with neovascular AMD become legally blind despite
30 current therapy with anti-VEGF agents such as Lucentis®.

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The pharmacological approaches for treating loss of vision in dry AMD caused by underlying RPE damage vary, but they are all directed to controlling the mechanisms believed to initially cause the damage (e.g. the complement system) rather than reversing the damage caused by the loss of RPE cells. Alternative approaches under investigation involve transplantation of induced pluripotent stem cells or mature RPE cells.

Drusen are tiny yellow or white accumulations of extracellular material that build up between Bruch's membrane and the retinal pigment epithelium of the eye. The presence of drusen is the hallmark of age-related macular degeneration. Recent studies of drusen, have implicated a role for inflammation and other immune-mediated processes, in particular complement activation, in the aetiology of early and late forms of AMD. EP 2 302 076 discloses that Factor H protein (HF1), the major inhibitor of the alternative complement pathway, accumulates within drusen, and is synthesized locally by the retinal pigment epithelium and thus provides the administration of a medicament that decreases the amount of a variant Factor H or expression of a gene encoding Factor H in an amount effective to reduce a symptom of AMD in the patient.

US 9'815'819 B2 relates to compounds that modulate, and preferably inhibit, activation of the alternative complement pathway as a method of treating or preventing AMD.

WO 2015/138628 relates to AAV vector constructs that are capable of, and optimized for, delivering anti-

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inflammatory peptides to the retina of AMD patients.

AU 2019/226198 discloses a method of producing a substantially purified culture of RPE cells suitable for transplantation.

5 CN 103656742 relates to a preparation method of functionalized retinal pigment epithelial cell grafts for transplantation to the retina of AMD patients.

RU 2628697 discloses a procedure to produce a cell layer from retinal pigment epithelial cells in a convenient and
10 stable manner without using an artificial membrane and leading to high rate of engraftment when transplanted intraocularly.

PCT/US19/68768 describes the application of small molecules for triggering endogenous regeneration of
15 photoreceptors derived from retinal stem and progenitor cells in retinal dystrophies i.e. retinitis pigmentosa. In contrast, the present invention relates to the treatment and/or prevention of RPE-related ocular diseases by stimulating pigmentation and/or growth of mammalian RPE
20 cells.

In the case of wet AMD, there has been great progress in the development of drugs that antagonize the effects of vascular endothelial growth factor (anti-VEGF). However, these treatments do not address the damage of the RPE
25 layer but only suppress neovascularization. Also, they are not curative but only effective at keeping the current state of the disease.

The problem of the present invention is therefore to

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provide therapeutic agents for the treatment and/or prevention of RPE-related diseases and particularly for the treatment of AMD.

The problem is solved by a compound of formula (I).
5 Further preferred embodiments are subject of the dependent claims.

It has been shown that the new compounds of formula (I) stimulate pigmentation and/or growth of mammalian RPE cells. This stimulation of pigmentation and/or growth of
10 the endogenous RPE cells allows a controlled repair and regeneration of the retina. Thus, it is possible to prevent vision loss and/or restore vision by endogenously generating new healthy RPE cells by a compound according to the present invention. Therefore, the compound of
15 formula I is useful as a therapeutically active substance in the treatment and/or prevention of diseases leading to atrophy, death or degeneration of the retinal pigment epithelium, i.e. as a medicament.

The term "RPE cells" encompasses in this context any form
20 of proliferative and non-proliferative retinal pigment epithelial cells that can support or give rise to further differentiated functional tissues of the eye. RPE cells are smooth, pigmented and hexagonal in shape. Healthy and fully differentiated RPE cells build melanosomes, which
25 contain the light-absorbing pigment melanin. Compounds that promote the differentiation of healthy and functional RPE cells hence lead to the presence of pigmentation.

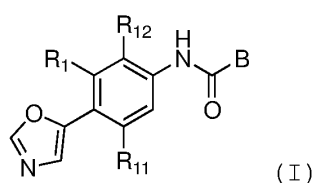
The term "growth of mammalian RPE cells" stands for the controlled promotion of RPE cell proliferation and a

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corresponding increase in RPE cell numbers.

The term "prevention" refers to the prevention or reduction of signs and symptoms associated with RPE-related diseases, in particular of macular degeneration leading to vision loss in subjects who are at risk for developing the disease. In these subjects a predisposing factor may be retained, but the signs and/or symptoms of the disease do not occur or take significantly longer to develop. Further, it also includes the prevention of a further deterioration of the symptoms once the disease has occurred.

Thus, the present invention relates to a method of treating and/or preventing a disease involving the retinal pigment epithelium, comprising administering the compound of formula (I)

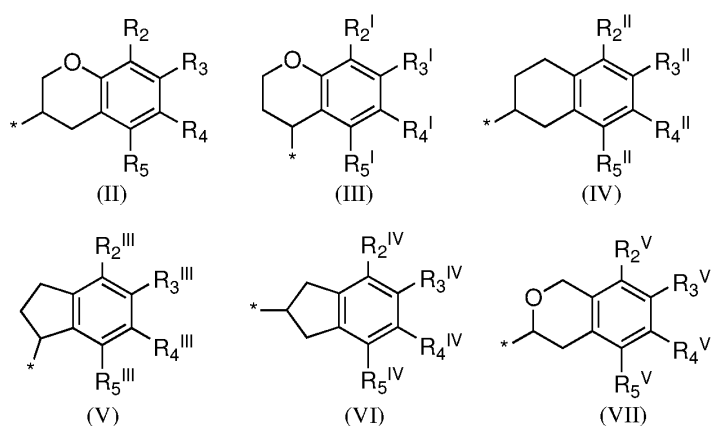


or a pharmaceutically acceptable salt, a racemic mixture, a corresponding enantiomer or, if applicable, a corresponding diastereomer thereof,

wherein:

R_1 , R_{11} and R_{12} are independently selected from the group consisting of hydrogen, fluoro, chloro, methoxy, trifluoromethyl, methyl, dimethylaminoethoxy and difluoromethoxy, whereby at least one of R_1 , R_{11} and R_{12} is not hydrogen,

B is selected from the group consisting of a residue of formula (II), (III), (IV), (V), (VI), (VII)



wherein,

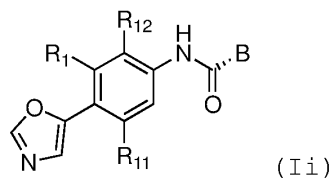
- 5 "*" denotes the point of attachment to the remainder of the molecule, and

R₂, R₃, R₄, R₅, R₂^I, R₃^I, R₄^I, R₅^I, R₂^{II}, R₃^{II}, R₄^{II}, R₅^{II}, R₂^{III}, R₃^{III}, R₄^{III}, R₅^{III}, R₂^{IV}, R₃^{IV}, R₄^{IV}, R₅^{IV}, R₂^V, R₃^V, R₄^V, R₅^V are independently selected from the group consisting of
 10 hydrogen, a linear or branched alkyl having 1 to 3 carbon atoms, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, trifluoromethyl and difluoromethoxy.

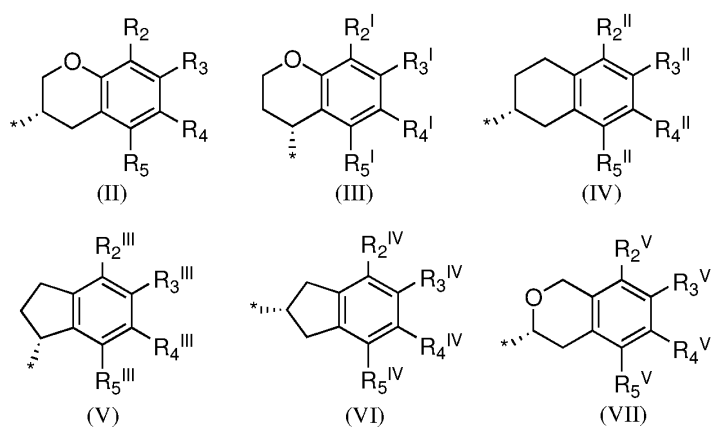
The term "pharmaceutically acceptable salt" stands for therapeutically active, non-toxic acid salt forms, which
 15 the compound according to the present invention is able to form.

In one embodiment of the present invention the asymmetric center at ring position * of the residue of formula (II), (III), (IV), (V), (VI) and (VII) has the configuration as
 20 depicted below, that is a compound of formula (Ii)

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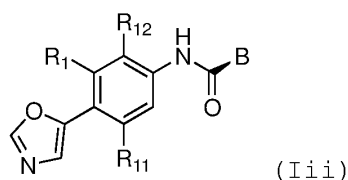


and B is selected from the group consisting of a residue of formula (II), (III), (IV), (V), (VII)



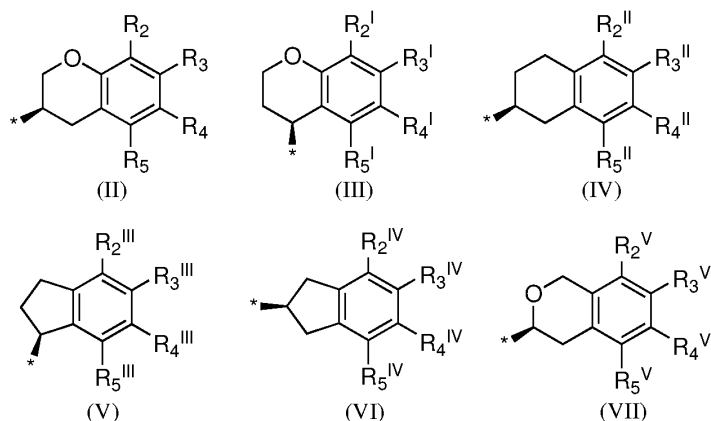
5 and R_2 , R_3 , R_4 , R_5 , R_2^I , R_3^I , R_4^I , R_5^I , R_2^{II} , R_3^{II} , R_4^{II} , R_5^{II} , R_2^{III} , R_3^{III} , R_4^{III} , R_5^{III} , R_2^{IV} , R_3^{IV} , R_4^{IV} , R_5^{IV} , R_2^V , R_3^V , R_4^V , R_5^V have the same definition as above.

In another embodiment of the present invention the asymmetric center at ring position * of the residue of
 10 formula (II), (III), (IV), (V), (VI) and (VII) is in the configuration as depicted below, that is a compound of formula (Iii)



and B is selected from the group consisting of a residue

of formula (II), (III), (IV), (V), (VI) and (VII)



and R₂, R₃, R₄, R₅, R₂^I, R₃^I, R₄^I, R₅^I, R₂^{II}, R₃^{II}, R₄^{II}, R₅^{II},
 5 R₂^{III}, R₃^{III}, R₄^{III}, R₅^{III}, R₂^{IV}, R₃^{IV}, R₄^{IV}, R₅^{IV}, R₂^V, R₃^V, R₄^V, R₅^V
 have the same definition as above.

Thus, the residue B can be unsubstituted, monosubstituted or polysubstituted. The term "unsubstituted" means that all residues of B are hydrogen. The term "monosubstituted"
 10 means that one of the residues of B is not hydrogen and the term "polysubstituted" means that at least two of the residues of B are not hydrogen.

Preferably, the residue B is unsubstituted or monosubstituted.

15 Preferably, in the residue B of the compound of formula (I), the residues R₃, R₄, R₃^I, R₄^I, R₃^{II}, R₄^{II}, R₃^{III}, R₄^{III}, R₃^{IV}, R₄^{IV}, R₃^V, R₄^V are independently selected from the group consisting of hydrogen, chloro, fluoro, methoxy and ethoxy.

20 In one embodiment, the residues R₂, R₃, R₅, R₂^I, R₃^I, R₅^I, R₂^{II}, R₃^{II}, R₅^{II}, R₂^{III}, R₃^{III}, R₅^{III}, R₂^{IV}, R₃^{IV}, R₅^{IV}, R₂^V, R₃^V, R₅^V

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are hydrogen and R_4 , R_4^I , R_4^{II} , R_4^{III} , R_4^{IV} , R_4^V are selected from the group consisting of fluoro, chloro, methoxy, and ethoxy.

In another embodiment, in the monosubstituted residue B of
5 the compound of formula (I), the residues R_2 , R_4 , R_5 , R_2^I , R_4^I , R_5^I , R_2^{II} , R_4^{II} , R_5^{II} , R_2^{III} , R_4^{III} , R_5^{III} , R_2^{IV} , R_4^{IV} , R_5^{IV} , R_2^V , R_4^V , R_5^V are hydrogen and R_3 , R_3^I , R_3^{II} , R_3^{III} , R_3^{IV} , R_3^V are selected from the group consisting of fluoro, chloro, methoxy, and ethoxy.

10 In a further embodiment, in the compound of the present invention, R_1 is chloro or methoxy, R_{11} and R_{12} are both hydrogen, and the residue B is unsubstituted or monosubstituted, preferably monosubstituted. Said compounds show an outstanding biological activity.

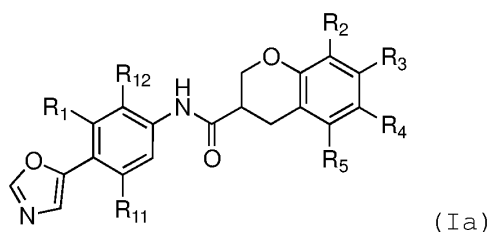
15 In a further aspect of the present invention, in the compound of the present invention, R_{12} is methyl, difluoromethoxy or dimethylamino-ethoxy, R_1 and R_{11} are both hydrogen, and the residue B is unsubstituted or monosubstituted.

20 In a further aspect of the present invention, in the compound of the present invention, R_1 is methyl or trifluoromethyl, R_{12} and R_{11} are both hydrogen, and the residue B is unsubstituted or monosubstituted.

In a further aspect of the present invention, in the
25 compound of the present invention, R_1 and R_{11} are independently from each other chloro, fluoro or methoxy, R_{12} is hydrogen, and the residue B is unsubstituted or monosubstituted.

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One embodiment of the present invention relates to the compound of formula (Ia)



or a pharmaceutically acceptable salt, a racemic mixture,
5 a corresponding enantiomer or, if applicable, a
corresponding diastereomer thereof,

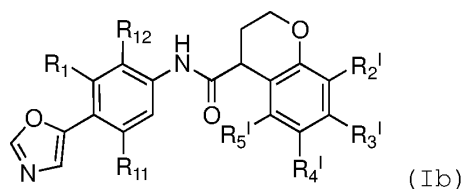
wherein:

R₁, R₁₁, R₁₂, R₂, R₃, R₄ and R₅ have the same definition as
above. Preferably, the residue B in formula Ia is
10 unsubstituted or monosubstituted. Most preferably, R₁ is
chloro, R₁₁ and R₁₂ are hydrogen, and the residue B is
unsubstituted.

Alternatively preferred, R₁ is chloro, R₁₁ and R₁₂ are
hydrogen, and the residue B is monosubstituted, where R₂
15 and R₅ are hydrogen, and one of R₃ or R₄ is hydrogen and
the other residue is selected from the group consisting of
fluoro, chloro, methoxy and ethoxy, i.e., the residue B is
monosubstituted and either R₃ or R₄ is selected from the
group consisting of fluoro, chloro, methoxy and ethoxy.

20 Another embodiment of the present invention relates to the
compound of formula (Ib)

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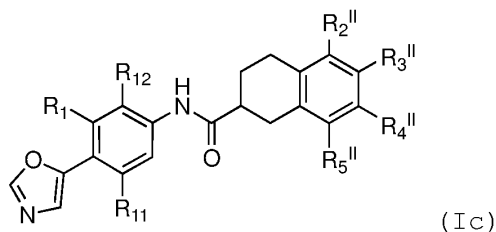
or a pharmaceutically acceptable salt, a racemic mixture, a corresponding enantiomer or, if applicable, a corresponding diastereomer thereof,

5 wherein:

R_1 , R_{11} , R_{12} , R_2^I , R_3^I , R_4^I and R_5^I have the same definition as above. Preferably, the residue B in formula Ib is unsubstituted or monosubstituted. Most preferably, R_1 is chloro, R_{11} and R_{12} is hydrogen, and the residue B is
10 unsubstituted.

Alternatively preferred, R_1 is chloro, R_{11} and R_{12} is hydrogen, and the residue B is monosubstituted, where R_2^I and R_5^I are hydrogen, and one of R_3^I or R_4^I is hydrogen and the other residue is selected from the group consisting of
15 fluoro, chloro, methoxy and ethoxy, i.e., the residue B is monosubstituted and either R_3^I or R_4^I is selected from the group consisting of fluoro, chloro, methoxy and ethoxy.

Another embodiment of the present invention relates to the compound of formula (Ic)



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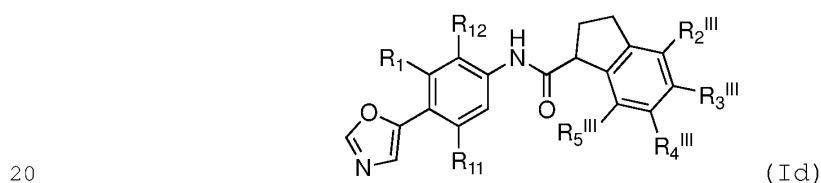
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or a pharmaceutically acceptable salt, a racemic mixture, a corresponding enantiomer or, if applicable, a corresponding diastereomer thereof,

wherein:

- 5 R_1 , R_{11} , R_{12} , R_2^{II} , R_3^{II} , R_4^{II} and R_5^{II} have the same definition as above. Preferably, the residue B in formula Ic is unsubstituted or monosubstituted. Most preferably, R_1 is chloro, R_{11} and R_{12} is hydrogen, and the residue B is unsubstituted.
- 10 Alternatively preferred, R_1 is chloro, R_{11} and R_{12} is hydrogen, and the residue B is monosubstituted, where R_2^{II} and R_5^{II} are hydrogen, and one of R_3^{II} or R_4^{II} is hydrogen and the other residue is selected from the group consisting of fluoro, chloro, methoxy and ethoxy, i.e.,
- 15 the residue B is monosubstituted and either R_3^{II} or R_4^{II} is selected from the group consisting of fluoro, chloro, methoxy and ethoxy.

Another embodiment of the present invention relates to the compound of formula (Id)



or a pharmaceutically acceptable salt, a racemic mixture, a corresponding enantiomer or, if applicable, a corresponding diastereomer thereof,

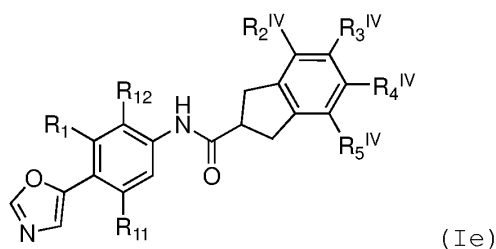
wherein:

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R_1 , R_{11} , R_{12} , R_2^{III} , R_3^{III} , R_4^{III} and R_5^{III} have the same definition as above. Preferably, the residue B in formula Id is unsubstituted or monosubstituted. Most preferably, R_1 is chloro, R_{11} and R_{12} is hydrogen, and the residue B is unsubstituted.

Alternatively preferred, R_1 is chloro, R_{11} and R_{12} is hydrogen, and the residue B is monosubstituted, where R_2^{III} and R_5^{III} are hydrogen, and one of R_3^{III} or R_4^{III} is hydrogen and the other residue is selected from the group consisting of fluoro, chloro, methoxy and ethoxy, i.e., the residue B is monosubstituted and either R_3^{III} or R_4^{III} is selected from the group consisting of fluoro, chloro, methoxy and ethoxy.

Another embodiment of the present invention relates to the compound of formula (Ie)



or a pharmaceutically acceptable salt, a racemic mixture, a corresponding enantiomer or, if applicable, a corresponding diastereomer thereof,

wherein:

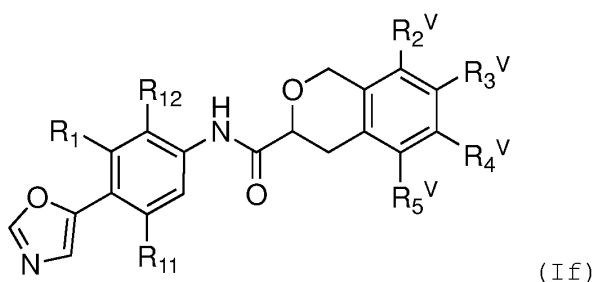
R_1 , R_{11} , R_{12} , R_2^{IV} , R_3^{IV} , R_4^{IV} and R_5^{IV} have the same definition as above. Preferably, the residue B in formula Ie is

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unsubstituted or monosubstituted. Most preferably, R_1 is chloro, R_{11} and R_{12} is hydrogen, and the residue B is unsubstituted.

Alternatively preferred, R_1 is chloro, R_{11} and R_{12} is hydrogen, and the residue B is monosubstituted, where R_2^{IV} and R_5^{IV} are hydrogen, and one of R_3^{IV} or R_4^{IV} is hydrogen and the other residue is selected from the group consisting of fluoro, chloro, methoxy and ethoxy, i.e., the residue B is monosubstituted and either R_3^{IV} or R_4^{IV} is selected from the group consisting of fluoro, chloro, methoxy and ethoxy.

Another embodiment of the present invention relates to the compound of formula (If)



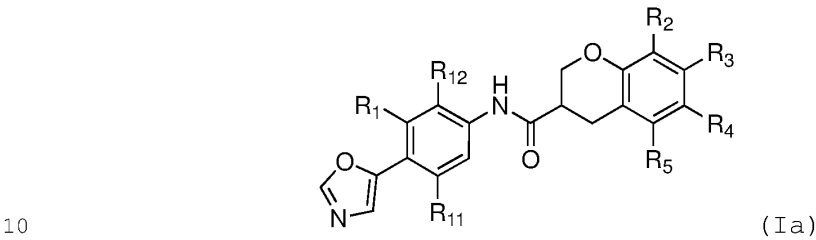
or a pharmaceutically acceptable salt, a racemic mixture, a corresponding enantiomer or, if applicable, a corresponding diastereomer thereof,

wherein:

R_1 , R_{11} , R_{12} , R_2^V , R_3^V , R_4^V and R_5^V have the same definition as above. Preferably, the residue B in formula If is unsubstituted or monosubstituted. Most preferably, R_1 is chloro, R_{11} and R_{12} is hydrogen, and the residue B is unsubstituted.

Alternatively preferred, R₁ is chloro, R₁₁ and R₁₂ is hydrogen, and the residue B is monosubstituted, where R₂^V and R₅^V are hydrogen, and and one of R₃^V or R₄^V is hydrogen and the other residue is selected from the group consisting of fluoro, chloro, methoxy and ethoxy, i.e., the residue B is monosubstituted and either R₃^V or R₄^V is selected from the group consisting of fluoro, chloro, methoxy and ethoxy.

Preferably, the compound of formula (Ia)



is selected from the group consisting of compounds of the formula (I), wherein R₁, R₁₁, R₁₂, R₂, R₃, R₄ and R₅ are as indicated in Table 1:

Table 1:						
R ₁	R ₁₁	R ₁₂	R ₂	R ₃	R ₄	R ₅
CF ₃	H	H	F	H	H	H
CF ₃	H	H	H	CH ₃	H	H
CF ₃	H	H	H	F	H	H
CF ₃	H	H	H	H	F	H
CF ₃	H	H	H	H	H	OCH ₃
CF ₃	H	H	H	H	Cl	H
CF ₃	H	H	H	H	OCH ₃	H
CH ₃	H	H	F	H	H	H
CH ₃	H	H	H	CH ₃	H	H
CH ₃	H	H	H	F	H	H
CH ₃	H	H	H	H	F	H
CH ₃	H	H	H	H	H	OCH ₃
CH ₃	H	H	H	H	Cl	H
CH ₃	H	H	H	H	OCH ₃	H
Cl	H	H	F	H	F	H
Cl	H	H	F	H	H	H

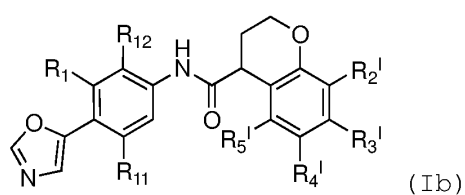
Cl	H	H	H	CH ₃	H	H
Cl	H	H	H	F	F	H
Cl	H	H	H	F	H	H
Cl	H	H	H	H	Cl	H
Cl	H	H	H	H	F	H
Cl	H	H	H	H	H	OCF ₂ H
Cl	H	H	H	H	H	OCH ₃
Cl	H	H	H	H	OCF ₂ H	H
Cl	H	H	H	H	OCH ₃	H
F	H	H	F	H	H	H
F	H	H	H	CH ₃	H	H
F	H	H	H	F	H	H
F	H	H	H	H	F	H
F	H	H	H	H	H	OCH ₃
F	H	H	H	H	Cl	H
F	H	H	H	H	OCH ₃	H
H	H	CF ₃	F	H	H	H
H	H	CF ₃	H	CH ₃	H	H
H	H	CF ₃	H	F	H	H
H	H	CF ₃	H	H	F	H
H	H	CF ₃	H	H	H	OCH ₃
H	H	CF ₃	H	H	Cl	H
H	H	CF ₃	H	H	OCH ₃	H
H	H	CH ₃	F	H	H	H
H	H	CH ₃	H	CH ₃	H	H
H	H	CH ₃	H	F	H	H
H	H	CH ₃	H	H	F	H
H	H	CH ₃	H	H	H	OCH ₃
H	H	CH ₃	H	H	Cl	H
H	H	CH ₃	H	H	OCH ₃	H
H	H	OCF ₂ H	F	H	H	H
H	H	OCF ₂ H	H	CH ₃	H	H
H	H	OCF ₂ H	H	F	H	H
H	H	OCF ₂ H	H	H	F	H
H	H	OCF ₂ H	H	H	H	OCH ₃
H	H	OCF ₂ H	H	H	Cl	H
H	H	OCF ₂ H	H	H	OCH ₃	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	F	H	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	CH ₃	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	F	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	F	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	H	OCH ₃
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	Cl	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	OCH ₃	H
OCF ₂ H	H	H	F	H	H	H
OCF ₂ H	H	H	H	CH ₃	H	H
OCF ₂ H	H	H	H	F	H	H
OCF ₂ H	H	H	H	H	F	H
OCF ₂ H	H	H	H	H	H	OCH ₃

OCF ₂ H	H	H	H	H	Cl	H
OCF ₂ H	H	H	H	H	OCH ₃	H
OCH ₃	H	H	F	H	H	H
OCH ₃	H	H	H	CH ₃	H	H
OCH ₃	H	H	H	F	H	H
OCH ₃	H	H	H	H	F	H
OCH ₃	H	H	H	H	H	OCH ₃
OCH ₃	H	H	H	H	Cl	H
OCH ₃	H	H	H	H	OCH ₃	H
CF ₃	F	H	F	H	H	H
CF ₃	F	H	H	CH ₃	H	H
CF ₃	F	H	H	F	H	H
CF ₃	F	H	H	H	F	H
CF ₃	F	H	H	H	H	OCH ₃
CF ₃	F	H	H	H	Cl	H
CF ₃	F	H	H	H	OCH ₃	H
CH ₃	F	H	F	H	H	H
CH ₃	F	H	H	CH ₃	H	H
CH ₃	F	H	H	F	H	H
CH ₃	F	H	H	H	F	H
CH ₃	F	H	H	H	H	OCH ₃
CH ₃	F	H	H	H	Cl	H
CH ₃	F	H	H	H	OCH ₃	H
Cl	F	H	F	H	F	H
Cl	F	H	F	H	H	H
Cl	F	H	H	CH ₃	H	H
Cl	F	H	H	F	F	H
Cl	F	H	H	F	H	H
Cl	F	H	H	H	Cl	H
Cl	F	H	H	H	F	H
Cl	F	H	H	H	H	OCF ₂ H
Cl	F	H	H	H	H	OCH ₃
F	F	H	F	H	H	H
F	F	H	H	CH ₃	H	H
F	F	H	H	F	H	H
F	F	H	H	H	F	H
F	F	H	H	H	H	OCH ₃
F	F	H	H	H	Cl	H
F	F	H	H	H	OCH ₃	H
H	F	CF ₃	F	H	H	H
H	F	CF ₃	H	CH ₃	H	H
H	F	CF ₃	H	F	H	H
H	F	CF ₃	H	H	F	H
H	F	CF ₃	H	H	H	OCH ₃
H	F	CF ₃	H	H	Cl	H
H	F	CF ₃	H	H	OCH ₃	H
H	F	CH ₃	F	H	H	H
H	F	CH ₃	H	CH ₃	H	H
H	F	CH ₃	H	F	H	H

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H	F	CH ₃	H	H	F	H
H	F	CH ₃	H	H	H	OCH ₃
H	F	CH ₃	H	H	Cl	H
H	F	CH ₃	H	H	OCH ₃	H
H	F	OCF ₂ H	F	H	H	H
H	F	OCF ₂ H	H	CH ₃	H	H
H	F	OCF ₂ H	H	F	H	H
H	F	OCF ₂ H	H	H	F	H
H	F	OCF ₂ H	H	H	H	OCH ₃
H	F	OCF ₂ H	H	H	Cl	H
H	F	OCF ₂ H	H	H	OCH ₃	H
OCF ₂ H	F	H	F	H	H	H
OCF ₂ H	F	H	H	CH ₃	H	H
OCF ₂ H	F	H	H	F	H	H
OCF ₂ H	F	H	H	H	F	H
OCF ₂ H	F	H	H	H	H	OCH ₃
OCF ₂ H	F	H	H	H	Cl	H
OCF ₂ H	F	H	H	H	OCH ₃	H
OCH ₃	F	H	F	H	H	H
OCH ₃	F	H	H	CH ₃	H	H
OCH ₃	F	H	H	F	H	H
OCH ₃	F	H	H	H	F	H
OCH ₃	F	H	H	H	H	OCH ₃
OCH ₃	F	H	H	H	Cl	H
OCH ₃	F	H	H	H	OCH ₃	H

Preferably, the compound of formula (Ib)



- 5 is selected from the group consisting of compounds of the formula (I), wherein R₁, R₁₁, R₁₂, R₂^I, R₃^I, R₄^I and R₅^I are as indicated in Table 2:

Table 2:						
R ₁	R ₁₁	R ₁₂	R ₂ ^I	R ₃ ^I	R ₄ ^I	R ₅ ^I
CF ₃	H	H	F	H	H	H

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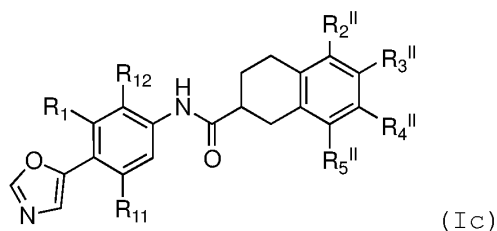
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CF ₃	H	H	H	F	H	H
CF ₃	H	H	H	H	F	H
CF ₃	H	H	H	H	H	OCH ₃
CF ₃	H	H	H	H	Cl	H
CF ₃	H	H	H	H	OCH ₃	H
CH ₃	H	H	F	H	H	H
CH ₃	H	H	H	CH ₃	H	H
CH ₃	H	H	H	F	H	H
CH ₃	H	H	H	H	F	H
CH ₃	H	H	H	H	H	OCH ₃
CH ₃	H	H	H	H	Cl	H
CH ₃	H	H	H	H	OCH ₃	H
Cl	H	H	F	H	F	H
Cl	H	H	F	H	H	H
Cl	H	H	H	CH ₃	H	H
Cl	H	H	H	F	F	H
Cl	H	H	H	F	H	H
Cl	H	H	H	H	Cl	H
Cl	H	H	H	H	F	H
Cl	H	H	H	H	H	OCF ₂ H
Cl	H	H	H	H	H	OCH ₃
Cl	H	H	H	H	OCF ₂ H	H
Cl	H	H	H	H	OCH ₃	H
F	H	H	F	H	H	H
F	H	H	H	CH ₃	H	H
F	H	H	H	F	H	H
F	H	H	H	H	F	H
F	H	H	H	H	H	OCH ₃
F	H	H	H	H	Cl	H
F	H	H	H	H	OCH ₃	H
H	H	CF ₃	F	H	H	H
H	H	CF ₃	H	CH ₃	H	H
H	H	CF ₃	H	F	H	H
H	H	CF ₃	H	H	F	H
H	H	CF ₃	H	H	H	OCH ₃
H	H	CF ₃	H	H	Cl	H
H	H	CF ₃	H	H	OCH ₃	H
H	H	CH ₃	F	H	H	H
H	H	CH ₃	H	CH ₃	H	H
H	H	CH ₃	H	F	H	H
H	H	CH ₃	H	H	F	H
H	H	CH ₃	H	H	H	OCH ₃
H	H	CH ₃	H	H	Cl	H
H	H	CH ₃	H	H	OCH ₃	H
H	H	OCF ₂ H	F	H	H	H
H	H	OCF ₂ H	H	CH ₃	H	H
H	H	OCF ₂ H	H	F	H	H
H	H	OCF ₂ H	H	H	F	H

H	H	OCF ₂ H	H	H	H	OCH ₃
H	H	OCF ₂ H	H	H	Cl	H
H	H	OCF ₂ H	H	H	OCH ₃	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	F	H	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	CH ₃	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	F	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	F	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	H	OCH ₃
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	Cl	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	OCH ₃	H
OCF ₂ H	H	H	F	H	H	H
OCF ₂ H	H	H	H	CH ₃	H	H
OCF ₂ H	H	H	H	F	H	H
OCF ₂ H	H	H	H	H	F	H
OCF ₂ H	H	H	H	H	H	OCH ₃
OCF ₂ H	H	H	H	H	Cl	H
OCF ₂ H	H	H	H	H	OCH ₃	H
OCH ₃	H	H	F	H	H	H
OCH ₃	H	H	H	CH ₃	H	H
OCH ₃	H	H	H	F	H	H
OCH ₃	H	H	H	H	F	H
OCH ₃	H	H	H	H	H	OCH ₃
OCH ₃	H	H	H	H	Cl	H
OCH ₃	H	H	H	H	OCH ₃	H
CF ₃	F	H	F	H	H	H
CF ₃	F	H	H	CH ₃	H	H
CF ₃	F	H	H	F	H	H
CF ₃	F	H	H	H	F	H
CF ₃	F	H	H	H	H	OCH ₃
CF ₃	F	H	H	H	Cl	H
CF ₃	F	H	H	H	OCH ₃	H
CH ₃	F	H	F	H	H	H
CH ₃	F	H	H	CH ₃	H	H
CH ₃	F	H	H	F	H	H
CH ₃	F	H	H	H	F	H
CH ₃	F	H	H	H	H	OCH ₃
CH ₃	F	H	H	H	Cl	H
CH ₃	F	H	H	H	OCH ₃	H
Cl	F	H	F	H	F	H
Cl	F	H	F	H	H	H
Cl	F	H	H	CH ₃	H	H
Cl	F	H	H	F	F	H
Cl	F	H	H	F	H	H
Cl	F	H	H	H	Cl	H
Cl	F	H	H	H	F	H
Cl	F	H	H	H	H	OCF ₂ H
Cl	F	H	H	H	H	OCH ₃
F	F	H	F	H	H	H
F	F	H	H	CH ₃	H	H

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F	F	H	H	F	H	H
F	F	H	H	H	F	H
F	F	H	H	H	H	OCH ₃
F	F	H	H	H	Cl	H
F	F	H	H	H	OCH ₃	H
H	F	CF ₃	F	H	H	H
H	F	CF ₃	H	CH ₃	H	H
H	F	CF ₃	H	F	H	H
H	F	CF ₃	H	H	F	H
H	F	CF ₃	H	H	H	OCH ₃
H	F	CF ₃	H	H	Cl	H
H	F	CF ₃	H	H	OCH ₃	H
H	F	CH ₃	F	H	H	H
H	F	CH ₃	H	CH ₃	H	H
H	F	CH ₃	H	F	H	H
H	F	CH ₃	H	H	F	H
H	F	CH ₃	H	H	H	OCH ₃
H	F	CH ₃	H	H	Cl	H
H	F	CH ₃	H	H	OCH ₃	H
H	F	OCF ₂ H	F	H	H	H
H	F	OCF ₂ H	H	CH ₃	H	H
H	F	OCF ₂ H	H	F	H	H
H	F	OCF ₂ H	H	H	F	H
H	F	OCF ₂ H	H	H	H	OCH ₃
H	F	OCF ₂ H	H	H	Cl	H
H	F	OCF ₂ H	H	H	OCH ₃	H
OCF ₂ H	F	H	F	H	H	H
OCF ₂ H	F	H	H	CH ₃	H	H
OCF ₂ H	F	H	H	F	H	H
OCF ₂ H	F	H	H	H	F	H
OCF ₂ H	F	H	H	H	H	OCH ₃
OCF ₂ H	F	H	H	H	Cl	H
OCF ₂ H	F	H	H	H	OCH ₃	H
OCH ₃	F	H	F	H	H	H
OCH ₃	F	H	H	CH ₃	H	H
OCH ₃	F	H	H	F	H	H
OCH ₃	F	H	H	H	F	H
OCH ₃	F	H	H	H	H	OCH ₃
OCH ₃	F	H	H	H	Cl	H
OCH ₃	F	H	H	H	OCH ₃	H

Preferably, the compound of formula (Ic)



is selected from the group consisting of compounds of the formula (I), wherein R_1 , R_{11} , R_{12} , R_2^{II} , R_3^{II} , R_4^{II} and R_5^{II} are as indicated in Table 3:

Table 3:						
R_1	R_{11}	R_{12}	R_2^{II}	R_3^{II}	R_4^{II}	R_5^{II}
CF ₃	H	H	F	H	H	H
CF ₃	H	H	H	CH ₃	H	H
CF ₃	H	H	H	F	H	H
CF ₃	H	H	H	H	F	H
CF ₃	H	H	H	H	H	OCH ₃
CF ₃	H	H	H	H	Cl	H
CF ₃	H	H	H	H	OCH ₃	H
CH ₃	H	H	F	H	H	H
CH ₃	H	H	H	CH ₃	H	H
CH ₃	H	H	H	F	H	H
CH ₃	H	H	H	H	F	H
CH ₃	H	H	H	H	H	OCH ₃
CH ₃	H	H	H	H	Cl	H
CH ₃	H	H	H	H	OCH ₃	H
Cl	H	H	F	H	F	H
Cl	H	H	F	H	H	H
Cl	H	H	H	CH ₃	H	H
Cl	H	H	H	F	F	H
Cl	H	H	H	F	H	H
Cl	H	H	H	H	Cl	H
Cl	H	H	H	H	F	H
Cl	H	H	H	H	H	OCF ₂ H
Cl	H	H	H	H	H	OCH ₃
Cl	H	H	H	H	OCF ₂ H	H
Cl	H	H	H	OCH ₃	H	H
F	H	H	F	H	H	H
F	H	H	H	CH ₃	H	H
F	H	H	H	F	H	H
F	H	H	H	H	F	H
F	H	H	H	H	H	OCH ₃
F	H	H	H	H	Cl	H
F	H	H	H	H	OCH ₃	H

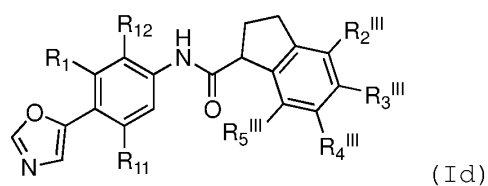
H	H	CF ₃	F	H	H	H
H	H	CF ₃	H	CH ₃	H	H
H	H	CF ₃	H	F	H	H
H	H	CF ₃	H	H	F	H
H	H	CF ₃	H	H	H	OCH ₃
H	H	CF ₃	H	H	Cl	H
H	H	CF ₃	H	H	OCH ₃	H
H	H	CH ₃	F	H	H	H
H	H	CH ₃	H	CH ₃	H	H
H	H	CH ₃	H	F	H	H
H	H	CH ₃	H	H	F	H
H	H	CH ₃	H	H	H	OCH ₃
H	H	CH ₃	H	H	Cl	H
H	H	CH ₃	H	H	OCH ₃	H
H	H	OCF ₂ H	F	H	H	H
H	H	OCF ₂ H	H	CH ₃	H	H
H	H	OCF ₂ H	H	F	H	H
H	H	OCF ₂ H	H	H	F	H
H	H	OCF ₂ H	H	H	H	OCH ₃
H	H	OCF ₂ H	H	H	Cl	H
H	H	OCF ₂ H	H	H	OCH ₃	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	F	H	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	CH ₃	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	F	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	F	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	H	OCH ₃
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	Cl	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	OCH ₃	H
OCF ₂ H	H	H	F	H	H	H
OCF ₂ H	H	H	H	CH ₃	H	H
OCF ₂ H	H	H	H	F	H	H
OCF ₂ H	H	H	H	H	F	H
OCF ₂ H	H	H	H	H	H	OCH ₃
OCF ₂ H	H	H	H	H	Cl	H
OCF ₂ H	H	H	H	H	OCH ₃	H
OCH ₃	H	H	F	H	H	H
OCH ₃	H	H	H	CH ₃	H	H
OCH ₃	H	H	H	F	H	H
OCH ₃	H	H	H	H	F	H
OCH ₃	H	H	H	H	H	OCH ₃
OCH ₃	H	H	H	H	Cl	H
OCH ₃	H	H	H	H	OCH ₃	H
CF ₃	F	H	F	H	H	H
CF ₃	F	H	H	CH ₃	H	H
CF ₃	F	H	H	F	H	H
CF ₃	F	H	H	H	F	H
CF ₃	F	H	H	H	H	OCH ₃
CF ₃	F	H	H	H	Cl	H
CF ₃	F	H	H	H	OCH ₃	H

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CH ₃	F	H	F	H	H	H
CH ₃	F	H	H	CH ₃	H	H
CH ₃	F	H	H	F	H	H
CH ₃	F	H	H	H	F	H
CH ₃	F	H	H	H	H	OCH ₃
CH ₃	F	H	H	H	Cl	H
CH ₃	F	H	H	H	OCH ₃	H
Cl	F	H	F	H	F	H
Cl	F	H	F	H	H	H
Cl	F	H	H	CH ₃	H	H
Cl	F	H	H	F	F	H
Cl	F	H	H	F	H	H
Cl	F	H	H	H	Cl	H
Cl	F	H	H	H	F	H
Cl	F	H	H	H	H	OCF ₂ H
Cl	F	H	H	H	H	OCH ₃
F	F	H	F	H	H	H
F	F	H	H	CH ₃	H	H
F	F	H	H	F	H	H
F	F	H	H	H	F	H
F	F	H	H	H	H	OCH ₃
F	F	H	H	H	Cl	H
F	F	H	H	H	OCH ₃	H
H	F	CF ₃	F	H	H	H
H	F	CF ₃	H	CH ₃	H	H
H	F	CF ₃	H	F	H	H
H	F	CF ₃	H	H	F	H
H	F	CF ₃	H	H	H	OCH ₃
H	F	CF ₃	H	H	Cl	H
H	F	CF ₃	H	H	OCH ₃	H
H	F	CH ₃	F	H	H	H
H	F	CH ₃	H	CH ₃	H	H
H	F	CH ₃	H	F	H	H
H	F	CH ₃	H	H	F	H
H	F	CH ₃	H	H	H	OCH ₃
H	F	CH ₃	H	H	Cl	H
H	F	CH ₃	H	H	OCH ₃	H
H	F	OCF ₂ H	F	H	H	H
H	F	OCF ₂ H	H	CH ₃	H	H
H	F	OCF ₂ H	H	F	H	H
H	F	OCF ₂ H	H	H	F	H
H	F	OCF ₂ H	H	H	H	OCH ₃
H	F	OCF ₂ H	H	H	Cl	H
H	F	OCF ₂ H	H	H	OCH ₃	H
OCF ₂ H	F	H	F	H	H	H
OCF ₂ H	F	H	H	CH ₃	H	H
OCF ₂ H	F	H	H	F	H	H
OCF ₂ H	F	H	H	H	F	H
OCF ₂ H	F	H	H	H	H	OCH ₃

OCF ₂ H	F	H	H	H	Cl	H
OCF ₂ H	F	H	H	H	OCH ₃	H
OCH ₃	F	H	F	H	H	H
OCH ₃	F	H	H	CH ₃	H	H
OCH ₃	F	H	H	F	H	H
OCH ₃	F	H	H	H	F	H
OCH ₃	F	H	H	H	H	OCH ₃
OCH ₃	F	H	H	H	Cl	H
OCH ₃	F	H	H	H	OCH ₃	H

5 Preferably, the compound of formula (Id)



is selected from the group consisting of compounds of the formula (I), wherein A, R₁, R₁₂, R₂^{III}, R₃^{III}, R₄^{III} and R₅^{III} are as indicated in Table 4:

Table 4:						
R ₁	R ₁₁	R ₁₂	R ₂ ^{III}	R ₃ ^{III}	R ₄ ^{III}	R ₅ ^{III}
CF ₃	H	H	F	H	H	H
CF ₃	H	H	H	CH ₃	H	H
CF ₃	H	H	H	F	H	H
CF ₃	H	H	H	H	F	H
CF ₃	H	H	H	H	H	OCH ₃
CF ₃	H	H	H	H	Cl	H
CF ₃	H	H	H	H	OCH ₃	H
CH ₃	H	H	F	H	H	H
CH ₃	H	H	H	CH ₃	H	H
CH ₃	H	H	H	F	H	H
CH ₃	H	H	H	H	F	H
CH ₃	H	H	H	H	H	OCH ₃

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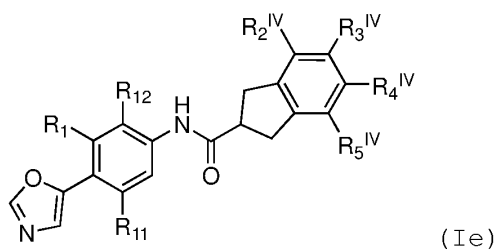
CH ₃	H	H	H	H	Cl	H
CH ₃	H	H	H	H	OCH ₃	H
Cl	H	H	F	H	F	H
Cl	H	H	F	H	H	H
Cl	H	H	H	CH ₃	H	H
Cl	H	H	H	F	F	H
Cl	H	H	H	F	H	H
Cl	H	H	H	H	Cl	H
Cl	H	H	H	H	F	H
Cl	H	H	H	H	H	OCF ₂ H
Cl	H	H	H	H	H	OCH ₃
Cl	H	H	H	H	OCF ₂ H	H
Cl	H	H	H	H	OCH ₃	H
F	H	H	F	H	H	H
F	H	H	H	CH ₃	H	H
F	H	H	H	F	H	H
F	H	H	H	H	F	H
F	H	H	H	H	H	OCH ₃
F	H	H	H	H	Cl	H
F	H	H	H	H	OCH ₃	H
H	H	CF ₃	F	H	H	H
H	H	CF ₃	H	CH ₃	H	H
H	H	CF ₃	H	F	H	H
H	H	CF ₃	H	H	F	H
H	H	CF ₃	H	H	H	OCH ₃
H	H	CF ₃	H	H	Cl	H
H	H	CF ₃	H	H	OCH ₃	H
H	H	CH ₃	F	H	H	H
H	H	CH ₃	H	CH ₃	H	H
H	H	CH ₃	H	F	H	H
H	H	CH ₃	H	H	F	H
H	H	CH ₃	H	H	H	OCH ₃
H	H	CH ₃	H	H	Cl	H
H	H	CH ₃	H	H	OCH ₃	H
H	H	OCF ₂ H	F	H	H	H
H	H	OCF ₂ H	H	CH ₃	H	H
H	H	OCF ₂ H	H	F	H	H
H	H	OCF ₂ H	H	H	F	H
H	H	OCF ₂ H	H	H	H	OCH ₃
H	H	OCF ₂ H	H	H	Cl	H
H	H	OCF ₂ H	H	H	OCH ₃	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	F	H	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	CH ₃	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	F	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	F	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	H	OCH ₃
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	Cl	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	OCH ₃	H
OCF ₂ H	H	H	F	H	H	H

OCF ₂ H	H	H	H	CH ₃	H	H
OCF ₂ H	H	H	H	F	H	H
OCF ₂ H	H	H	H	H	F	H
OCF ₂ H	H	H	H	H	H	OCH ₃
OCF ₂ H	H	H	H	H	Cl	H
OCF ₂ H	H	H	H	H	OCH ₃	H
OCH ₃	H	H	F	H	H	H
OCH ₃	H	H	H	CH ₃	H	H
OCH ₃	H	H	H	F	H	H
OCH ₃	H	H	H	H	F	H
OCH ₃	H	H	H	H	H	OCH ₃
OCH ₃	H	H	H	H	Cl	H
OCH ₃	H	H	H	H	OCH ₃	H
CF ₃	F	H	F	H	H	H
CF ₃	F	H	H	CH ₃	H	H
CF ₃	F	H	H	F	H	H
CF ₃	F	H	H	H	F	H
CF ₃	F	H	H	H	H	OCH ₃
CF ₃	F	H	H	H	Cl	H
CF ₃	F	H	H	H	OCH ₃	H
CH ₃	F	H	F	H	H	H
CH ₃	F	H	H	CH ₃	H	H
CH ₃	F	H	H	F	H	H
CH ₃	F	H	H	H	F	H
CH ₃	F	H	H	H	H	OCH ₃
CH ₃	F	H	H	H	Cl	H
CH ₃	F	H	H	H	OCH ₃	H
Cl	F	H	F	H	F	H
Cl	F	H	F	H	H	H
Cl	F	H	H	CH ₃	H	H
Cl	F	H	H	F	F	H
Cl	F	H	H	F	H	H
Cl	F	H	H	H	Cl	H
Cl	F	H	H	H	F	H
Cl	F	H	H	H	H	OCF ₂ H
Cl	F	H	H	H	H	OCH ₃
F	F	H	F	H	H	H
F	F	H	H	CH ₃	H	H
F	F	H	H	F	H	H
F	F	H	H	H	F	H
F	F	H	H	H	H	OCH ₃
F	F	H	H	H	Cl	H
F	F	H	H	H	OCH ₃	H
H	F	CF ₃	F	H	H	H
H	F	CF ₃	H	CH ₃	H	H
H	F	CF ₃	H	F	H	H
H	F	CF ₃	H	H	F	H
H	F	CF ₃	H	H	H	OCH ₃
H	F	CF ₃	H	H	Cl	H

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H	F	CF ₃	H	H	OCH ₃	H
H	F	CH ₃	F	H	H	H
H	F	CH ₃	H	CH ₃	H	H
H	F	CH ₃	H	F	H	H
H	F	CH ₃	H	H	F	H
H	F	CH ₃	H	H	H	OCH ₃
H	F	CH ₃	H	H	Cl	H
H	F	CH ₃	H	H	OCH ₃	H
H	F	OCF ₂ H	F	H	H	H
H	F	OCF ₂ H	H	CH ₃	H	H
H	F	OCF ₂ H	H	F	H	H
H	F	OCF ₂ H	H	H	F	H
H	F	OCF ₂ H	H	H	H	OCH ₃
H	F	OCF ₂ H	H	H	Cl	H
H	F	OCF ₂ H	H	H	OCH ₃	H
OCF ₂ H	F	H	F	H	H	H
OCF ₂ H	F	H	H	CH ₃	H	H
OCF ₂ H	F	H	H	F	H	H
OCF ₂ H	F	H	H	H	F	H
OCF ₂ H	F	H	H	H	H	OCH ₃
OCF ₂ H	F	H	H	H	Cl	H
OCF ₂ H	F	H	H	H	OCH ₃	H
OCH ₃	F	H	F	H	H	H
OCH ₃	F	H	H	CH ₃	H	H
OCH ₃	F	H	H	F	H	H
OCH ₃	F	H	H	H	F	H
OCH ₃	F	H	H	H	H	OCH ₃
OCH ₃	F	H	H	H	Cl	H
OCH ₃	F	H	H	H	OCH ₃	H

Preferably, the compound of formula (Ie)



5

is selected from the group consisting of compounds of the

formula (I), wherein R_1 , R_{11} , R_{12} , R_2^{IV} , R_3^{IV} , R_4^{IV} and R_5^{IV} are as indicated in Table 5:

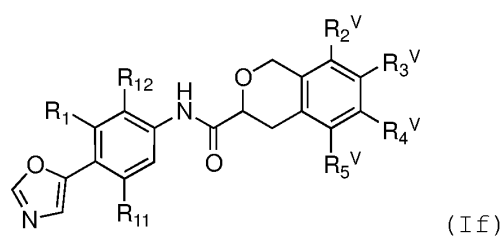
Table 5:						
R_1	R_{11}	R_{12}	R_2^{IV}	R_3^{IV}	R_4^{IV}	R_5^{IV}
CF ₃	H	H	F	H	H	H
CF ₃	H	H	H	CH ₃	H	H
CF ₃	H	H	H	F	H	H
CF ₃	H	H	H	H	F	H
CF ₃	H	H	H	H	H	OCH ₃
CF ₃	H	H	H	H	Cl	H
CF ₃	H	H	H	H	OCH ₃	H
CH ₃	H	H	F	H	H	H
CH ₃	H	H	H	CH ₃	H	H
CH ₃	H	H	H	F	H	H
CH ₃	H	H	H	H	F	H
CH ₃	H	H	H	H	H	OCH ₃
CH ₃	H	H	H	H	Cl	H
CH ₃	H	H	H	H	OCH ₃	H
Cl	H	H	F	H	F	H
Cl	H	H	F	H	H	H
Cl	H	H	H	CH ₃	H	H
Cl	H	H	H	F	F	H
Cl	H	H	H	F	H	H
Cl	H	H	H	H	Cl	H
Cl	H	H	H	H	F	H
Cl	H	H	H	H	H	OCF ₂ H
Cl	H	H	H	H	H	OCH ₃
Cl	H	H	H	H	OCF ₂ H	H
Cl	H	H	H	H	OCH ₃	H
F	H	H	F	H	H	H
F	H	H	H	CH ₃	H	H
F	H	H	H	F	H	H
F	H	H	H	H	F	H
F	H	H	H	H	H	OCH ₃
F	H	H	H	H	Cl	H
F	H	H	H	H	OCH ₃	H
H	H	CF ₃	F	H	H	H
H	H	CF ₃	H	CH ₃	H	H
H	H	CF ₃	H	F	H	H
H	H	CF ₃	H	H	F	H
H	H	CF ₃	H	H	H	OCH ₃
H	H	CF ₃	H	H	Cl	H
H	H	CF ₃	H	H	OCH ₃	H
H	H	CH ₃	F	H	H	H
H	H	CH ₃	H	CH ₃	H	H
H	H	CH ₃	H	F	H	H
H	H	CH ₃	H	H	F	H

H	H	CH ₃	H	H	H	OCH ₃
H	H	CH ₃	H	H	Cl	H
H	H	CH ₃	H	H	OCH ₃	H
H	H	OCF ₂ H	F	H	H	H
H	H	OCF ₂ H	H	CH ₃	H	H
H	H	OCF ₂ H	H	F	H	H
H	H	OCF ₂ H	H	H	F	H
H	H	OCF ₂ H	H	H	H	OCH ₃
H	H	OCF ₂ H	H	H	Cl	H
H	H	OCF ₂ H	H	H	OCH ₃	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	F	H	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	CH ₃	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	F	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	F	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	H	OCH ₃
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	Cl	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	OCH ₃	H
OCF ₂ H	H	H	F	H	H	H
OCF ₂ H	H	H	H	CH ₃	H	H
OCF ₂ H	H	H	H	F	H	H
OCF ₂ H	H	H	H	H	F	H
OCF ₂ H	H	H	H	H	H	OCH ₃
OCF ₂ H	H	H	H	H	Cl	H
OCF ₂ H	H	H	H	H	OCH ₃	H
OCH ₃	H	H	F	H	H	H
OCH ₃	H	H	H	CH ₃	H	H
OCH ₃	H	H	H	F	H	H
OCH ₃	H	H	H	H	F	H
OCH ₃	H	H	H	H	H	OCH ₃
OCH ₃	H	H	H	H	Cl	H
OCH ₃	H	H	H	H	OCH ₃	H
CF ₃	F	H	F	H	H	H
CF ₃	F	H	H	CH ₃	H	H
CF ₃	F	H	H	F	H	H
CF ₃	F	H	H	H	F	H
CF ₃	F	H	H	H	H	OCH ₃
CF ₃	F	H	H	H	Cl	H
CF ₃	F	H	H	H	OCH ₃	H
CH ₃	F	H	F	H	H	H
CH ₃	F	H	H	CH ₃	H	H
CH ₃	F	H	H	F	H	H
CH ₃	F	H	H	H	F	H
CH ₃	F	H	H	H	H	OCH ₃
CH ₃	F	H	H	H	Cl	H
CH ₃	F	H	H	H	OCH ₃	H
Cl	F	H	F	H	F	H
Cl	F	H	F	H	H	H
Cl	F	H	H	CH ₃	H	H
Cl	F	H	H	F	F	H

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Cl	F	H	H	F	H	H
Cl	F	H	H	H	Cl	H
Cl	F	H	H	H	F	H
Cl	F	H	H	H	H	OCF ₂ H
Cl	F	H	H	H	H	OCH ₃
F	F	H	F	H	H	H
F	F	H	H	CH ₃	H	H
F	F	H	H	F	H	H
F	F	H	H	H	F	H
F	F	H	H	H	H	OCH ₃
F	F	H	H	H	Cl	H
F	F	H	H	H	OCH ₃	H
H	F	CF ₃	F	H	H	H
H	F	CF ₃	H	CH ₃	H	H
H	F	CF ₃	H	F	H	H
H	F	CF ₃	H	H	F	H
H	F	CF ₃	H	H	H	OCH ₃
H	F	CF ₃	H	H	Cl	H
H	F	CF ₃	H	H	OCH ₃	H
H	F	CH ₃	F	H	H	H
H	F	CH ₃	H	CH ₃	H	H
H	F	CH ₃	H	F	H	H
H	F	CH ₃	H	H	F	H
H	F	CH ₃	H	H	H	OCH ₃
H	F	CH ₃	H	H	Cl	H
H	F	CH ₃	H	H	OCH ₃	H
H	F	OCF ₂ H	F	H	H	H
H	F	OCF ₂ H	H	CH ₃	H	H
H	F	OCF ₂ H	H	F	H	H
H	F	OCF ₂ H	H	H	F	H
H	F	OCF ₂ H	H	H	H	OCH ₃
H	F	OCF ₂ H	H	H	Cl	H
H	F	OCF ₂ H	H	H	OCH ₃	H
OCF ₂ H	F	H	F	H	H	H
OCF ₂ H	F	H	H	CH ₃	H	H
OCF ₂ H	F	H	H	F	H	H
OCF ₂ H	F	H	H	H	F	H
OCF ₂ H	F	H	H	H	H	OCH ₃
OCF ₂ H	F	H	H	H	Cl	H
OCF ₂ H	F	H	H	H	OCH ₃	H
OCH ₃	F	H	F	H	H	H
OCH ₃	F	H	H	CH ₃	H	H
OCH ₃	F	H	H	F	H	H
OCH ₃	F	H	H	H	F	H
OCH ₃	F	H	H	H	H	OCH ₃
OCH ₃	F	H	H	H	Cl	H
OCH ₃	F	H	H	H	OCH ₃	H

Preferably, the compound of formula (If)



- 5 is selected from the group consisting of compounds of the formula (I), wherein R_1 , R_{11} , R_{12} , R_2^V , R_3^V , R_4^V and R_5^V are as indicated in Table 6:

Table 6:						
R_1	R_{11}	R_{12}	R_2^V	R_3^V	R_4^V	R_5^V
CF_3	H	H	F	H	H	H
CF_3	H	H	H	CH_3	H	H
CF_3	H	H	H	F	H	H
CF_3	H	H	H	H	F	H
CF_3	H	H	H	H	H	OCH_3
CF_3	H	H	H	H	Cl	H
CF_3	H	H	H	H	OCH_3	H
CH_3	H	H	F	H	H	H
CH_3	H	H	H	CH_3	H	H
CH_3	H	H	H	F	H	H
CH_3	H	H	H	H	F	H
CH_3	H	H	H	H	H	OCH_3
CH_3	H	H	H	H	Cl	H
CH_3	H	H	H	H	OCH_3	H
Cl	H	H	F	H	F	H
Cl	H	H	F	H	H	H
Cl	H	H	H	CH_3	H	H
Cl	H	H	H	F	F	H
Cl	H	H	H	F	H	H
Cl	H	H	H	H	Cl	H
Cl	H	H	H	H	F	H
Cl	H	H	H	H	H	OCF_2H
Cl	H	H	H	H	H	OCH_3
Cl	H	H	H	H	OCF_2H	H
Cl	H	H	H	H	OCH_3	H

F	H	H	F	H	H	H
F	H	H	H	CH ₃	H	H
F	H	H	H	F	H	H
F	H	H	H	H	F	H
F	H	H	H	H	H	OCH ₃
F	H	H	H	H	Cl	H
F	H	H	H	H	OCH ₃	H
H	H	CF ₃	F	H	H	H
H	H	CF ₃	H	CH ₃	H	H
H	H	CF ₃	H	F	H	H
H	H	CF ₃	H	H	F	H
H	H	CF ₃	H	H	H	OCH ₃
H	H	CF ₃	H	H	Cl	H
H	H	CF ₃	H	H	OCH ₃	H
H	H	CH ₃	F	H	H	H
H	H	CH ₃	H	CH ₃	H	H
H	H	CH ₃	H	F	H	H
H	H	CH ₃	H	H	F	H
H	H	CH ₃	H	H	H	OCH ₃
H	H	CH ₃	H	H	Cl	H
H	H	CH ₃	H	H	OCH ₃	H
H	H	OCF ₂ H	F	H	H	H
H	H	OCF ₂ H	H	CH ₃	H	H
H	H	OCF ₂ H	H	F	H	H
H	H	OCF ₂ H	H	H	F	H
H	H	OCF ₂ H	H	H	H	OCH ₃
H	H	OCF ₂ H	H	H	Cl	H
H	H	OCF ₂ H	H	H	OCH ₃	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	F	H	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	CH ₃	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	F	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	F	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	H	OCH ₃
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	Cl	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	OCH ₃	H
OCF ₂ H	H	H	F	H	H	H
OCF ₂ H	H	H	H	CH ₃	H	H
OCF ₂ H	H	H	H	F	H	H
OCF ₂ H	H	H	H	H	F	H
OCF ₂ H	H	H	H	H	H	OCH ₃
OCF ₂ H	H	H	H	H	Cl	H
OCF ₂ H	H	H	H	H	OCH ₃	H
OCH ₃	H	H	F	H	H	H
OCH ₃	H	H	H	CH ₃	H	H
OCH ₃	H	H	H	F	H	H
OCH ₃	H	H	H	H	F	H
OCH ₃	H	H	H	H	H	OCH ₃
OCH ₃	H	H	H	H	Cl	H
OCH ₃	H	H	H	H	OCH ₃	H

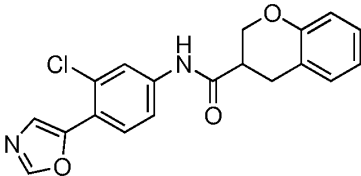
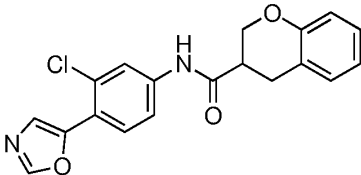
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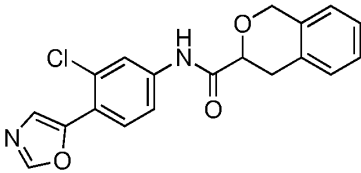
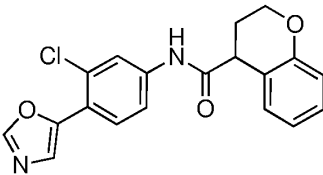
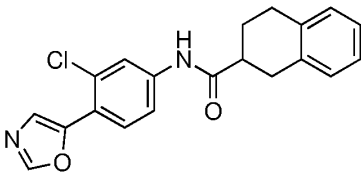
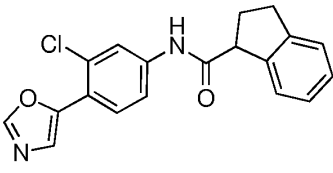
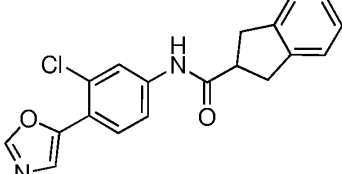
CF ₃	F	H	F	H	H	H
CF ₃	F	H	H	CH ₃	H	H
CF ₃	F	H	H	F	H	H
CF ₃	F	H	H	H	F	H
CF ₃	F	H	H	H	H	OCH ₃
CF ₃	F	H	H	H	Cl	H
CF ₃	F	H	H	H	OCH ₃	H
CH ₃	F	H	F	H	H	H
CH ₃	F	H	H	CH ₃	H	H
CH ₃	F	H	H	F	H	H
CH ₃	F	H	H	H	F	H
CH ₃	F	H	H	H	H	OCH ₃
CH ₃	F	H	H	H	Cl	H
CH ₃	F	H	H	H	OCH ₃	H
Cl	F	H	F	H	F	H
Cl	F	H	F	H	H	H
Cl	F	H	H	CH ₃	H	H
Cl	F	H	H	F	F	H
Cl	F	H	H	F	H	H
Cl	F	H	H	H	Cl	H
Cl	F	H	H	H	F	H
Cl	F	H	H	H	H	OCF ₂ H
Cl	F	H	H	H	H	OCH ₃
F	F	H	F	H	H	H
F	F	H	H	CH ₃	H	H
F	F	H	H	F	H	H
F	F	H	H	H	F	H
F	F	H	H	H	H	OCH ₃
F	F	H	H	H	Cl	H
F	F	H	H	H	OCH ₃	H
H	F	CF ₃	F	H	H	H
H	F	CF ₃	H	CH ₃	H	H
H	F	CF ₃	H	F	H	H
H	F	CF ₃	H	H	F	H
H	F	CF ₃	H	H	H	OCH ₃
H	F	CF ₃	H	H	Cl	H
H	F	CF ₃	H	H	OCH ₃	H
H	F	CH ₃	F	H	H	H
H	F	CH ₃	H	CH ₃	H	H
H	F	CH ₃	H	F	H	H
H	F	CH ₃	H	H	F	H
H	F	CH ₃	H	H	H	OCH ₃
H	F	CH ₃	H	H	Cl	H
H	F	CH ₃	H	H	OCH ₃	H
H	F	OCF ₂ H	F	H	H	H
H	F	OCF ₂ H	H	CH ₃	H	H
H	F	OCF ₂ H	H	F	H	H
H	F	OCF ₂ H	H	H	F	H
H	F	OCF ₂ H	H	H	H	OCH ₃

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H	F	OCF ₂ H	H	H	Cl	H
H	F	OCF ₂ H	H	H	OCH ₃	H
OCF ₂ H	F	H	F	H	H	H
OCF ₂ H	F	H	H	CH ₃	H	H
OCF ₂ H	F	H	H	F	H	H
OCF ₂ H	F	H	H	H	F	H
OCF ₂ H	F	H	H	H	H	OCH ₃
OCF ₂ H	F	H	H	H	Cl	H
OCF ₂ H	F	H	H	H	OCH ₃	H
OCH ₃	F	H	F	H	H	H
OCH ₃	F	H	H	CH ₃	H	H
OCH ₃	F	H	H	F	H	H
OCH ₃	F	H	H	H	F	H
OCH ₃	F	H	H	H	H	OCH ₃
OCH ₃	F	H	H	H	Cl	H
OCH ₃	F	H	H	H	OCH ₃	H

Epecially good results could be obtained by the following compounds according to the present invention:

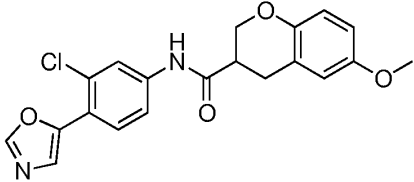
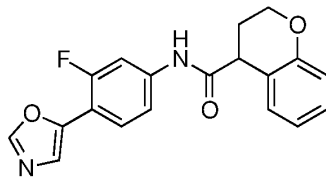
Table 7:		
Comp. No.	Chemical structure	Relative Pigmentation
1	 enantiomer with the shorter retention time from the chiral HPLC resolution	3.05
2	 enantiomer with the longer retention time from the chiral	1.68

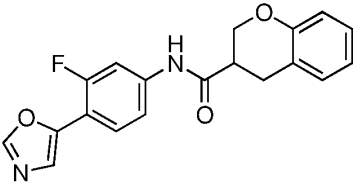
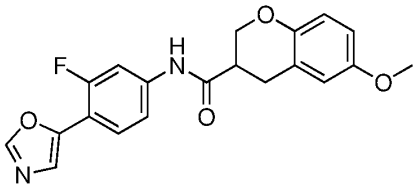
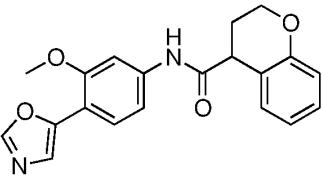
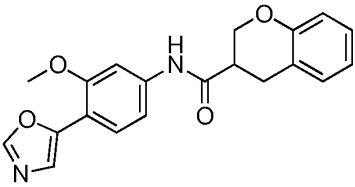
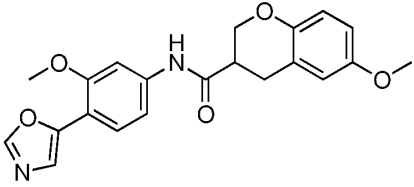
	HPLC resolution	
3	 (racemate)	1.66
4	 (racemate)	2.65
5	 (racemate)	1.18
6	 (racemate)	1.86
7	 (racemate)	2.92
C*	---	1

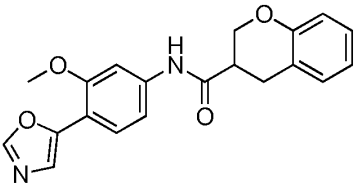
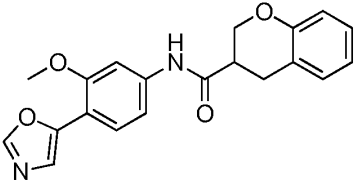
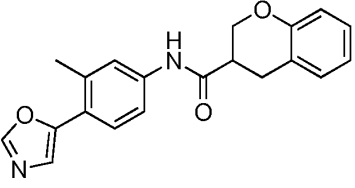
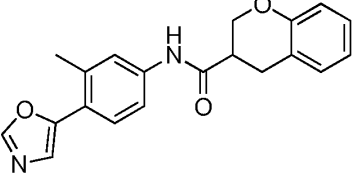
C* = Control experiment (absence of a compound according to the present invention).

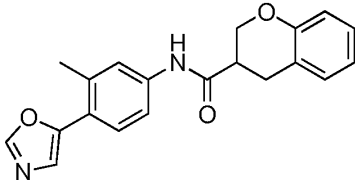
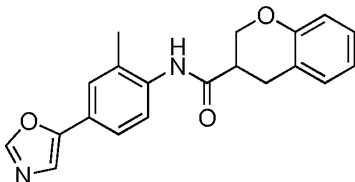
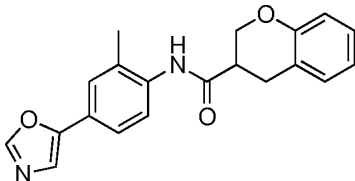
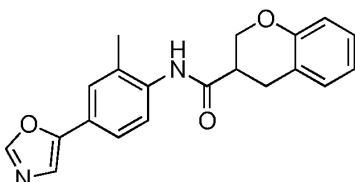
In particular, the compounds (1) and (7) show excellent results with regard to the pigmentation of RPE cells.

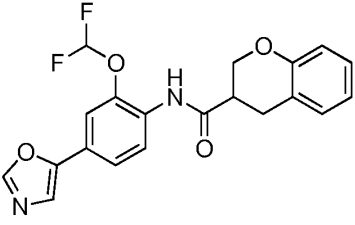
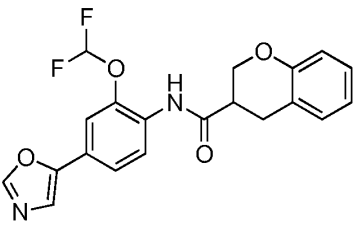
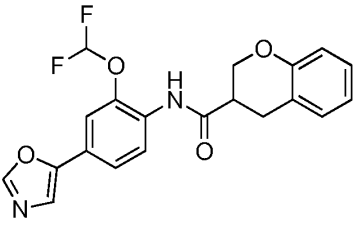
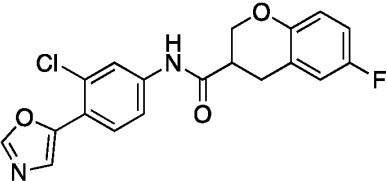
- 5 Further preferred compounds providing a good activity are depicted in Table 8. The expression "enantiomer with the shorter retention time from the chiral HPLC resolution" means that the enantiomer comes first in the chiral HPLC when applying the conditions described in the
- 10 corresponding Chiral Separation Method A, B, C, D, E, F, G, H, I and K below. Within the context of the present invention the enantiomer with the shorter retention time is also called "first enantiomer" and the one with the longer retention time "second enantiomer".

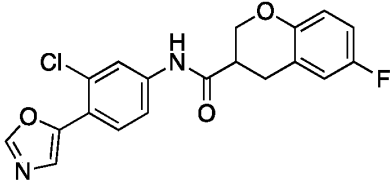
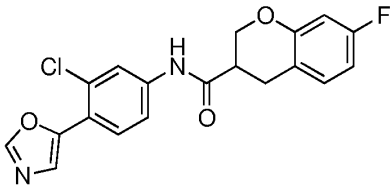
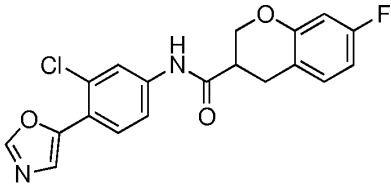
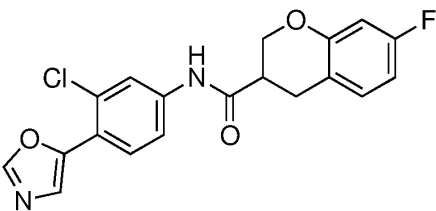
Table 8:	
Comp. No.	Chemical structure
8	 (racemate)
9	 (racemate)

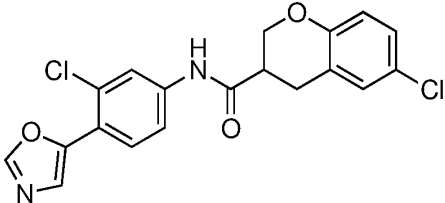
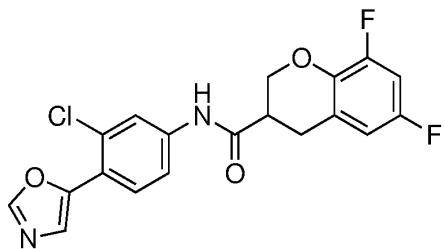
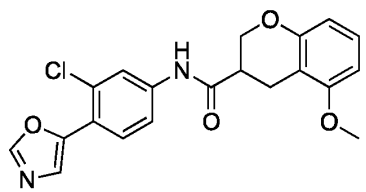
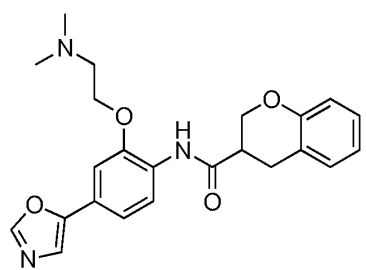
10	 (racemate)
11	 (racemate)
12	 (racemate)
13	 (racemate)
14	 (racemate)

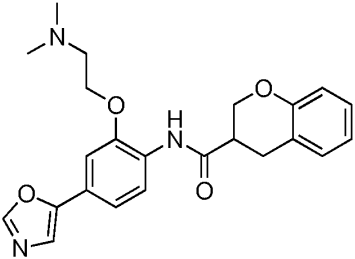
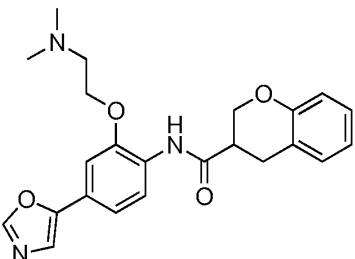
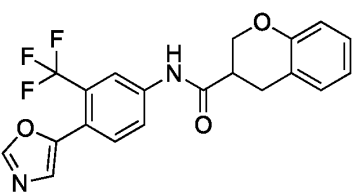
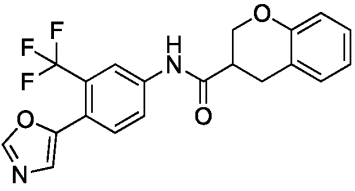
15	 enantiomer with the shorter retention time from the chiral HPLC resolution
16	 enantiomer with the longer retention time from the chiral HPLC resolution
17	 (racemate)
18	 enantiomer with the shorter retention time from the chiral HPLC resolution

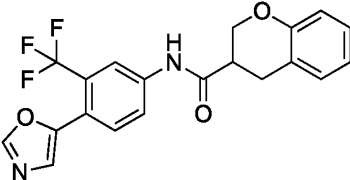
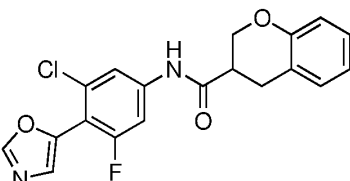
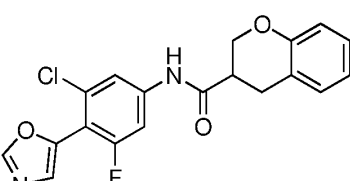
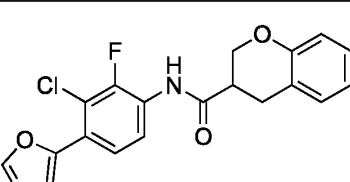
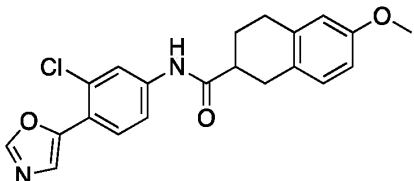
19	 enantiomer with the longer retention time from the chiral HPLC resolution
20	 (racemate)
21	 enantiomer with the shorter retention time from the chiral HPLC resolution
22	 enantiomer with the longer retention time from the chiral HPLC resolution

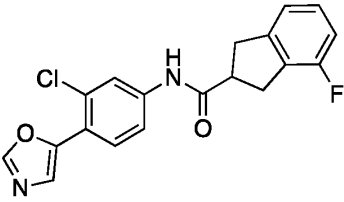
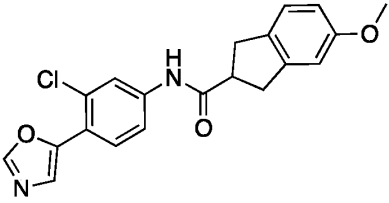
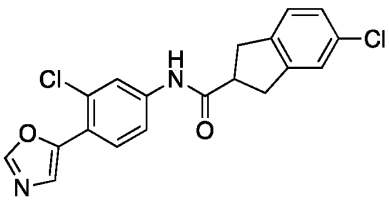
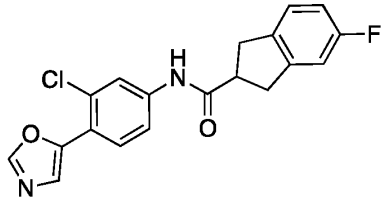
23	 (racemate)
24	 enantiomer with the shorter retention time from the chiral HPLC resolution
25	 enantiomer with the longer retention time from the chiral HPLC resolution
26	 enantiomer with the shorter retention time from the chiral HPLC resolution

27	 enantiomer with the longer retention time from the chiral HPLC resolution
28	 (racemate)
29	 enantiomer with the shorter retention time from the chiral HPLC resolution
30	 enantiomer with the longer retention time from the chiral HPLC resolution

31	 (racemate)
32	 (racemate)
33	 (racemate)
34	 (racemate)

35	 Chemical structure of an enantiomer with a shorter retention time from the chiral HPLC resolution. The structure features a central benzene ring substituted with a 4-isoxazol-5-yl group, a 2-(dimethylaminoethoxy) group, and a 2-(3,4-dihydro-2H-benzo[1,2-b:4,5-b']dioxol-2-yl)carbamoyl group.
36	 Chemical structure of an enantiomer with a longer retention time from the chiral HPLC resolution. The structure is identical to the one in row 35, featuring a central benzene ring substituted with a 4-isoxazol-5-yl group, a 2-(dimethylaminoethoxy) group, and a 2-(3,4-dihydro-2H-benzo[1,2-b:4,5-b']dioxol-2-yl)carbamoyl group.
37	 Chemical structure of a racemate. The structure features a central benzene ring substituted with a 4-isoxazol-5-yl group, a trifluoromethyl group, and a 2-(3,4-dihydro-2H-benzo[1,2-b:4,5-b']dioxol-2-yl)carbamoyl group. (racemate)
38	 Chemical structure of an enantiomer with a shorter retention time from the chiral HPLC resolution. The structure is identical to the one in row 37, featuring a central benzene ring substituted with a 4-isoxazol-5-yl group, a trifluoromethyl group, and a 2-(3,4-dihydro-2H-benzo[1,2-b:4,5-b']dioxol-2-yl)carbamoyl group.

39	 enantiomer with the longer retention time from the chiral HPLC resolution
40	 enantiomer with the shorter retention time from the chiral HPLC resolution
41	 enantiomer with the longer retention time from the chiral HPLC resolution
42	 (racemate)
43	

	(racemate)
44	 (racemate)
45	 (racemate)
46	 (racemate)
47	 (racemate)

As already mentioned, the compounds according to the present invention and the compositions according to the present invention stimulate the proliferation and/or

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differentiation of RPE cells. Thus, the compounds according to the present invention can be used in the treatment and/or prevention of RPE-related diseases, in particular of RPE diseases from the family of macular
5 degeneration leading to loss of vision. Most preferably, the disease is a disease leading to atrophy, degeneration or death of the retinal pigment epithelium that might further result in retinal neovascularization and/or death of photoreceptors.

10 Compounds and compositions according to the present invention are particularly useful in the treatment and/or prevention of disease selected from the group consisting of the family of macular degenerations consisting of early age-related macular degeneration (AMD), dry AMD and
15 geographic atrophy (GA) as well as wet AMD by inducing the proliferation and/or differentiation of RPE cells. Thus, due to the compounds and compositions of the present invention, it is possible to reverse RPE cell damage caused by an illness by restoring or regenerating
20 endogenous RPE cells, and not only to treat the loss of vision caused by RPE cell dysfunction and/or damage.

Compounds of formula (I) of the invention can be used, inter alia, to prevent the onset of dry age-related macular degeneration (dry AMD) and/or wet age-related
25 macular degeneration (wet AMD), to prevent the progression of early AMD to advanced forms of AMD including wet AMD or geographic atrophy (GA), to slow and/or prevent progression of GA, to prevent or reduce the loss of vision from AMD, and to improve vision lost due to pre-existing
30 early or advanced dry or wet AMD. It can also be used in

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combination with anti-VEGF therapies for the treatment of neovascular AMD patients or for the prevention of neovascular AMD.

Compounds and compositions according to the present invention are also useful in the treatment and/or prevention of disease selected from the group consisting of Best disease, autosomal recessive bestrophinopathy (ARB), gyrate atrophy, North Carolina macular dystrophy, central areolar choroidal dystrophy (CACD), Sorsby macular dystrophy, familial dominant drusen, cuticular or basal laminar drusen, retinopathy of prematurity, myopic degeneration, polypoidal choroidal vasculopathy (PCV), central serous retinopathy, angioid streaks, retinal detachment, retinal dialysis, Vogt-Koyanagi-Harada (VKH), acute posterior multifocal placoid pigment epitheliopathy (APMPPE), persistent placoid maculopathy (PPM) relentless placoid chorioretinopathy (RPC), serpiginous choroiditis, serpiginous-like choroiditis (multifocal serpiginoid choroiditis), multiple evanescence white dot syndrome (MEWDS) or Birdshot uveitis (vitiliginous chorioretinitis).

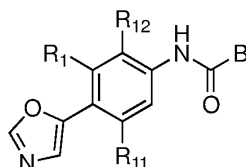
Compounds and compositions according to the present invention are particularly useful in the treatment and/or prevention of disease selected from the group consisting of a retinal disease leading to choroidal neovascularization or vascular leakage. Said retinal diseases are preferably selected from the group consisting of toxoplasmosis, toxocariasis, rubella, Behçets disease, choroidal hemangioma, trauma, choroidal rupture and idiopathic retinitis - vasculitis - aneurysms and

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neuroretinitis (IRVAN).

Compounds and compositions according to the present invention are particularly useful in the treatment and/or prevention of disease selected from the group consisting
5 of a retinal disease that causes retinal inflammation and degeneration like sympathetic ophthalmia, post-operative inflammation or non-arteritic ischemic optic neuropathy as well as retinal degeneration associated with systemic disease such as diabetes mellitus, sickle cell disease or
10 radiation retinopathy.

In a further embodiment, the present invention relates to a pharmaceutical composition for use in the treatment and/or prevention of a disease involving the retinal pigment epithelium, said pharmaceutical composition
15 comprising a pharmaceutically acceptable carrier and/or adjuvant; and a compound of the formula (I)

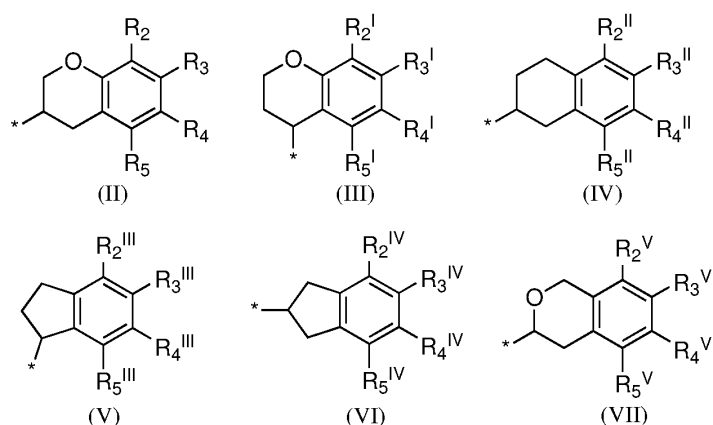


or a pharmaceutically acceptable salt, a racemic mixture, a corresponding enantiomer or, if applicable, a
20 corresponding diastereomer thereof,

wherein:

R₁, R₁₁ and R₁₂ are independently selected from the group consisting of hydrogen, fluoro, chloro, methoxy, trifluoromethyl, methyl and difluoromethoxy, whereby at
25 least one of R₁, R₁₁ and R₁₂ is not hydrogen,

B is selected from the group consisting of a residue of formula (II), (III), (IV), (V), (VI), (VII)



wherein,

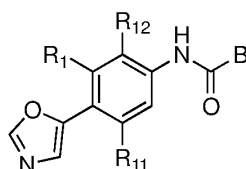
5 "*" denotes the point of attachment to the remainder of the molecule, and

R_2 , R_3 , R_4 , R_5 , R_2^I , R_3^I , R_4^I , R_5^I , R_2^{II} , R_3^{II} , R_4^{II} , R_5^{II} , R_2^{III} , R_3^{III} , R_4^{III} , R_5^{III} , R_2^{IV} , R_3^{IV} , R_4^{IV} , R_5^{IV} , R_2^V , R_3^V , R_4^V , R_5^V are independently selected from the group consisting of
 10 hydrogen, a linear or branched alkyl having 1 to 3 carbon atoms, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, trifluoromethyl and difluoromethoxy,

as a therapeutically active substance and a pharmaceutically acceptable carrier and/or adjuvant for
 15 use in the treatment and/or prevention of a disease involving the retinal pigment epithelium.

In a further embodiment, the present invention relates to a pharmaceutical composition for use in the treatment and/or prevention of a disease involving the retinal
 20 pigment epithelium, said pharmaceutical composition

comprising a pharmaceutically acceptable carrier and/or adjuvant; and a compound of the formula (I)

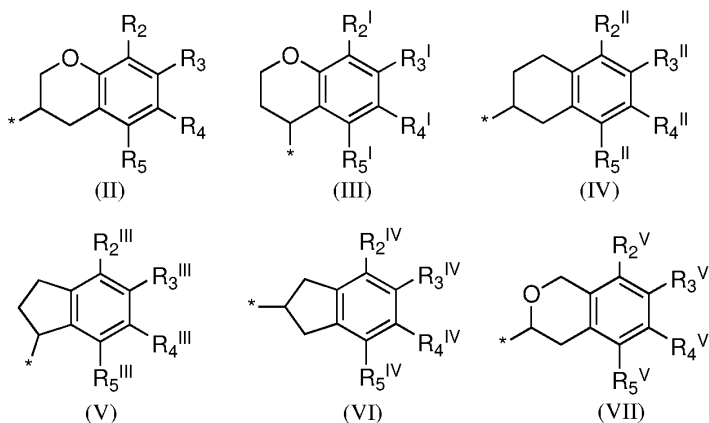


or a pharmaceutically acceptable salt, a racemic mixture,
 5 a corresponding enantiomer or, if applicable, a corresponding diastereomer thereof,

wherein:

R₁, R₁₁ and R₁₂ are independently selected from the group consisting of hydrogen, fluoro, chloro, methoxy,
 10 trifluoromethyl, methyl and difluoromethoxy, whereby at least one of R₁, R₁₁ and R₁₂ is not hydrogen,

B is selected from the group consisting of a residue of formula (II), (III), (IV), (V), (VI), (VII)



15 wherein,

"*" denotes the point of attachment to the remainder of the molecule, and

$R_2, R_3, R_4, R_5, R_2^I, R_3^I, R_4^I, R_5^I, R_2^{II}, R_3^{II}, R_4^{II}, R_5^{II}, R_2^{III}, R_3^{III}, R_4^{III}, R_5^{III}, R_2^{IV}, R_3^{IV}, R_4^{IV}, R_5^{IV}, R_2^V, R_3^V, R_4^V, R_5^V$ are
5 independently selected from the group consisting of hydrogen, a linear or branched alkyl having 1 to 3 carbon atoms, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, trifluoromethyl and difluoromethoxy,

with the proviso that if

- 10 a) R_{11} is hydrogen and
b) one of R_1 and R_{12} is selected from the group consisting of fluoro, chloro and methoxy, trifluoromethyl, methyl and difluoromethoxy, whereas the other of R_1 and R_{12} is hydrogen, then

15 B is either a residue of formula (IV) or (VII)

as a therapeutically active substance.

The compound or the composition according to the present invention can be administered to a patient, either alone or in combination with one or more additional therapeutic
20 agents. "Patient" as used herein, includes mammals such as humans, non-human primates, rats, mice, rabbits, hares, dogs, cats, horses, cows and pigs, preferably human.

The pharmaceutical composition according to the present invention may comprise one or more additional therapeutic
25 agents.

In a preferred embodiment of the present invention, the pharmaceutical composition comprises a pharmaceutically

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acceptable carrier and/or adjuvant; and a compound of the formula (I) as defined above, preferably a compound of formula (Ia), (Ib), (Ic), (Id), (Ie) or (If). Most preferably, it comprises a compound of formula (Ia), (Ib),
5 (Ic), (Id), (Ie) or (If) as disclosed in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, Table 7 and Table 8 above.

Preferably, such a pharmaceutical composition provides controlled release properties. The term "controlled
10 release pharmaceutical compositions" herein refers to any composition or dosage form, which comprises the compound of the present invention and which is formulated to provide a longer duration of pharmacological response after administration of the dosage form than is ordinarily
15 experienced after administration of a corresponding immediate release composition comprising the same drug in the same amount. Controlled release may be extended up to several months depending on the matrix used. Preferably, the release of the compound according to the present
20 invention takes place over a period of up to 12 months, most preferably over a period of up to 6 months. Such a controlled release formulation results in an increased patient comfort and in significant lower costs.

The matrix material used for a pharmaceutical composition
25 according to the present may comprise hydrophobic release controlling agents. It is preferably selected from but not limited to polyvinyl acetate dispersion, ethyl cellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate,
30 cellulose acetate butyrate, cellulose acetate phthalate,

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cellulose triacetate, poly (methyl methacrylate), poly (ethyl methacrylate), poly (butyl methacrylate), poly (isobutyl methacrylate), and poly (hexyl methacrylate), poly (isodecyl methacrylate), poly (lauryl methacrylate),
5 poly (phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl acrylate), poly (octadecyl acrylate), waxes such as beeswax, carnauba wax, paraffin wax, microcrystalline wax, and ozokerite; fatty alcohols such as cetostearyl alcohol, stearyl alcohol,
10 cetyl alcohol and myristyl alcohol, and fatty acid esters such as glyceryl monostearate; glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate, or hydrogenated vegetable oils.

15 The compound of the invention can be delivered to the eye through a variety of routes, including but not limited to topical application to the eye or by intraocular injection into, for example, the vitreous, subretinal (interphotoreceptor) or subconjunctival space; locally by
20 insertion or injection into the tissue surrounding the eye; systemically through an oral route or by subcutaneous, intravenous or intramuscular injection; or via catheter or implant. Most preferably, the compound of the present invention is delivered by intraocular
25 injection. Examples for topical ophthalmic compositions are eye drops, ointments, gels, solutions and suspensions.

The compound of the invention can be administered prior to the onset of the condition to prevent its occurrence, such as during eye surgery, immediately after the onset of the

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pathological condition, or during the occurrence of an acute or protracted condition.

Depending on the intended mode of administration, the compound according to the present invention may be incorporated in any pharmaceutically acceptable dosage form, such as for example, liquids, including solutions, suspensions and emulsions, tablets, suppositories, pills, capsules, powders or the like, preferably dosage forms suitable for single administration of precise dosages, or sustained release dosage forms for continuous controlled administration. Most preferred are liquids.

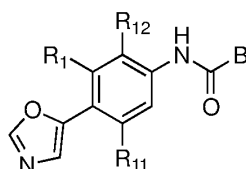
Liquid pharmaceutically administrable dosage forms can be for example a solution, a suspension or an emulsion, preferably a suspension comprising a compound of the present invention and optional pharmaceutical adjutants in a carrier, such as for example, water, saline, aqueous dextrose, glycerol, hyaluronic acid, ethanol, DMSO and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like. Typical examples of such auxiliary agents are sodium acetate, sorbitan monolaurate, triethanolamine, sodium acetate and triethanolamine oleate.

The present invention also relates to a method of the treating and/or preventing RPE-related diseases, comprising administering a compound of formula (I), preferably (Ia), (Ib), (Ic), (Id), (Ie) and (If) or a pharmaceutically acceptable salt, a racemic mixture, a

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corresponding enantiomer or, if applicable, a corresponding diastereomer thereof to a patient having the retinal disease so as to be delivered to an eye of the patient in an amount effective to treat the retinal
5 disease. The compounds of formula (Ia), (Ib), (Ic), (Id), (Ie) and (If) are defined above in detail.

In a further embodiment, the present invention relates new compound of the formula (I)

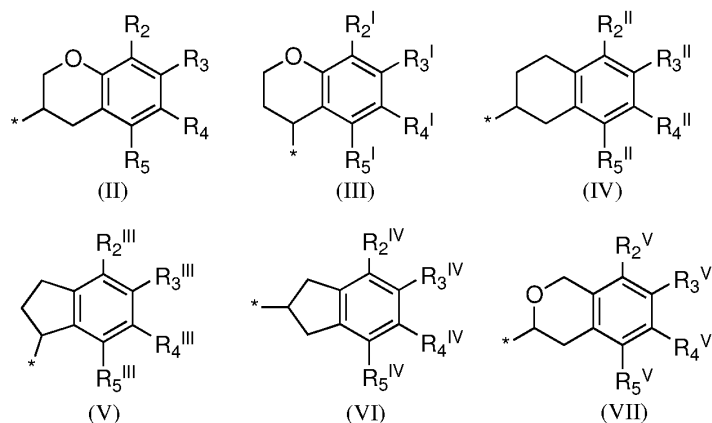


10 or a pharmaceutically acceptable salt, a racemic mixture, a corresponding enantiomer or, if applicable, a corresponding diastereomer thereof,

wherein:

R₁, R₁₁ and R₁₂ are independently selected from the group
15 consisting of hydrogen, fluoro, chloro, methoxy, trifluoromethyl, methyl and difluoromethoxy, whereby at least one of R₁, R₁₁ and R₁₂ is not hydrogen,

B is selected from the group consisting of a residue of formula (II), (III), (IV), (V), (VI), (VII)



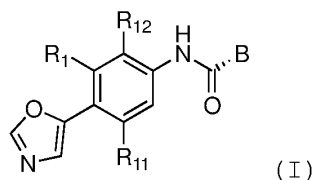
wherein,

"*" denotes the point of attachment to the remainder of the molecule, and

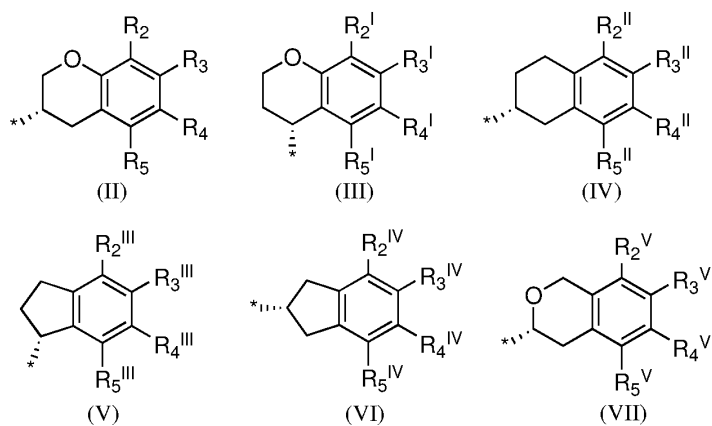
- 5 R₂, R₃, R₄, R₅, R₂^I, R₃^I, R₄^I, R₅^I, R₂^{II}, R₃^{II}, R₄^{II}, R₅^{II}, R₂^{III}, R₃^{III}, R₄^{III}, R₅^{III}, R₂^{IV}, R₃^{IV}, R₄^{IV}, R₅^{IV}, R₂^V, R₃^V, R₄^V, R₅^V are independently selected from the group consisting of hydrogen, a linear or branched alkyl having 1 to 3 carbon atoms, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, trifluoromethyl and difluoromethoxy
- 10

as a therapeutically active substance.

- In a further embodiment the present invention relates to a new compound of the formula (I), wherein the asymmetric center at ring position * of the residue of formula (II), (III), (IV), (V), (VI) and (VII) has the configuration as depicted below
- 15



and B is selected from the group consisting of a residue of formula (II), (III), (IV), (V), (VII)



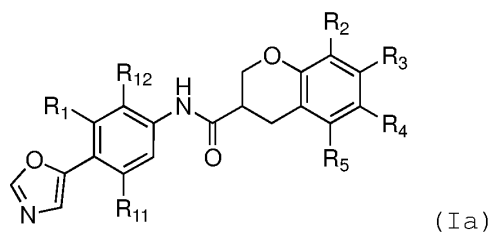
5 and R_2 , R_3 , R_4 , R_5 , R_2^I , R_3^I , R_4^I , R_5^I , R_2^{II} , R_3^{II} , R_4^{II} , R_5^{II} , R_2^{III} , R_3^{III} , R_4^{III} , R_5^{III} , R_2^{IV} , R_3^{IV} , R_4^{IV} , R_5^{IV} , R_2^V , R_3^V , R_4^V , R_5^V have the same definition as above,

with the proviso that if

- a) R_{11} is hydrogen and
- 10 b) one of R_1 and R_{12} is selected from the group consisting of fluoro, chloro and methoxy, trifluoromethyl, methyl and difluoromethoxy, whereas the other of R_1 and R_{12} is hydrogen, then

B is either a residue of formula (IV) or (VII).

15 In one embodiment of the present invention relates to compounds of (Ia)



selected from the group consisting of compounds of the formula (Ia) indicated in Table 11, wherein R_1 , R_{11} , R_{12} , R_2 , R_3 , R_4 and R_5 :

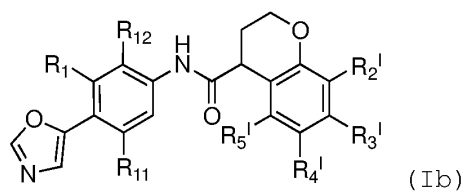
Table 11:						
R_1	R_{11}	R_{12}	R_2	R_3	R_4	R_5
CF ₃	H	H	F	H	H	H
CF ₃	H	H	H	H	F	H
CF ₃	H	H	H	H	Cl	H
CH ₃	H	H	H	H	F	H
CH ₃	H	H	H	H	Cl	H
Cl	H	H	H	F	F	H
F	H	H	F	H	H	H
F	H	H	H	H	F	H
F	H	H	H	H	Cl	H
OCF ₂ H	H	H	H	H	F	H
OCF ₂ H	H	H	H	H	Cl	H
OCH ₃	H	H	H	H	F	H
OCH ₃	H	H	H	H	Cl	H
H	H	CF ₃	F	H	H	H
H	H	CF ₃	H	H	F	H
H	H	CF ₃	H	H	Cl	H
H	H	CF ₃	H	H	OCH ₃	H
H	H	CH ₃	F	H	H	H
H	H	CH ₃	H	H	F	H
H	H	CH ₃	H	H	Cl	H
H	H	CH ₃	H	H	OCH ₃	H
H	H	OCF ₂ H	F	H	H	H
H	H	OCF ₂ H	H	H	F	H
H	H	OCF ₂ H	H	H	Cl	H
H	H	OCF ₂ H	H	H	OCH ₃	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	F	H	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	CH ₃	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	F	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	F	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	H	OCH ₃

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H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	Cl	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	OCH ₃	H
CF ₃	F	H	F	H	H	H
CF ₃	F	H	H	CH ₃	H	H
CF ₃	F	H	H	F	H	H
CF ₃	F	H	H	H	F	H
CF ₃	F	H	H	H	H	OCH ₃
CF ₃	F	H	H	H	Cl	H
CF ₃	F	H	H	H	OCH ₃	H
CH ₃	F	H	F	H	H	H
CH ₃	F	H	H	CH ₃	H	H
CH ₃	F	H	H	F	H	H
CH ₃	F	H	H	H	F	H
CH ₃	F	H	H	H	H	OCH ₃
CH ₃	F	H	H	H	Cl	H
CH ₃	F	H	H	H	OCH ₃	H
Cl	F	H	F	H	F	H
Cl	F	H	F	H	H	H
Cl	F	H	H	CH ₃	H	H
Cl	F	H	H	F	F	H
Cl	F	H	H	F	H	H
Cl	F	H	H	H	Cl	H
Cl	F	H	H	H	F	H
Cl	F	H	H	H	H	OCF ₂ H
Cl	F	H	H	H	H	OCH ₃
F	F	H	F	H	H	H
F	F	H	H	CH ₃	H	H
F	F	H	H	F	H	H
F	F	H	H	H	F	H
F	F	H	H	H	H	OCH ₃
F	F	H	H	H	Cl	H
F	F	H	H	H	OCH ₃	H
H	F	CF ₃	F	H	H	H
H	F	CF ₃	H	CH ₃	H	H
H	F	CF ₃	H	F	H	H
H	F	CF ₃	H	H	F	H
H	F	CF ₃	H	H	H	OCH ₃
H	F	CF ₃	H	H	Cl	H
H	F	CF ₃	H	H	OCH ₃	H
H	F	CH ₃	F	H	H	H
H	F	CH ₃	H	CH ₃	H	H
H	F	CH ₃	H	F	H	H
H	F	CH ₃	H	H	F	H
H	F	CH ₃	H	H	H	OCH ₃
H	F	CH ₃	H	H	Cl	H
H	F	CH ₃	H	H	OCH ₃	H
H	F	OCF ₂ H	F	H	H	H
H	F	OCF ₂ H	H	CH ₃	H	H
H	F	OCF ₂ H	H	F	H	H

H	F	OCF ₂ H	H	H	F	H
H	F	OCF ₂ H	H	H	H	OCH ₃
H	F	OCF ₂ H	H	H	Cl	H
H	F	OCF ₂ H	H	H	OCH ₃	H
OCF ₂ H	F	H	F	H	H	H
OCF ₂ H	F	H	H	CH ₃	H	H
OCF ₂ H	F	H	H	F	H	H
OCF ₂ H	F	H	H	H	F	H
OCF ₂ H	F	H	H	H	H	OCH ₃
OCF ₂ H	F	H	H	H	Cl	H
OCF ₂ H	F	H	H	H	OCH ₃	H
OCH ₃	F	H	F	H	H	H
OCH ₃	F	H	H	CH ₃	H	H
OCH ₃	F	H	H	F	H	H
OCH ₃	F	H	H	H	F	H
OCH ₃	F	H	H	H	H	OCH ₃
OCH ₃	F	H	H	H	Cl	H
OCH ₃	F	H	H	H	OCH ₃	H

In a further embodiment of the present invention relates to compounds of (Ib)



- 5 selected from the group consisting of compounds of the formula (Ia) indicated in Table 12, wherein R₁, R₁₁, R₁₂, R₂^I, R₃^I, R₄^I and R₅^I:

Table 12:						
R ₁	R ₁₁	R ₁₂	R ₂ ^I	R ₃ ^I	R ₄ ^I	R ₅ ^I
CF ₃	H	H	F	H	H	H
CF ₃	H	H	H	H	F	H
CF ₃	H	H	H	H	Cl	H
CH ₃	H	H	H	H	F	H
CH ₃	H	H	H	H	Cl	H
Cl	H	H	H	F	F	H
F	H	H	F	H	H	H
F	H	H	H	H	F	H

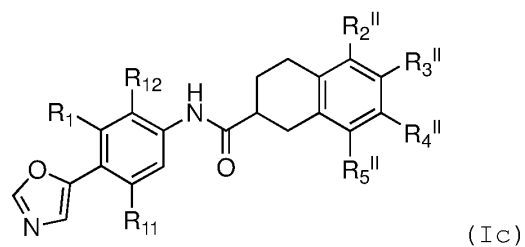
F	H	H	H	H	Cl	H
OCF ₂ H	H	H	H	H	F	H
OCF ₂ H	H	H	H	H	Cl	H
OCH ₃	H	H	H	H	F	H
OCH ₃	H	H	H	H	Cl	H
H	H	CF ₃	F	H	H	H
H	H	CF ₃	H	H	F	H
H	H	CF ₃	H	H	Cl	H
H	H	CF ₃	H	H	OCH ₃	H
H	H	CH ₃	F	H	H	H
H	H	CH ₃	H	H	F	H
H	H	CH ₃	H	H	Cl	H
H	H	CH ₃	H	H	OCH ₃	H
H	H	OCF ₂ H	F	H	H	H
H	H	OCF ₂ H	H	H	F	H
H	H	OCF ₂ H	H	H	Cl	H
H	H	OCF ₂ H	H	H	OCH ₃	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	F	H	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	CH ₃	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	F	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	F	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	H	OCH ₃
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	Cl	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	OCH ₃	H
CF ₃	F	H	F	H	H	H
CF ₃	F	H	H	CH ₃	H	H
CF ₃	F	H	H	F	H	H
CF ₃	F	H	H	H	F	H
CF ₃	F	H	H	H	H	OCH ₃
CF ₃	F	H	H	H	Cl	H
CF ₃	F	H	H	H	OCH ₃	H
CH ₃	F	H	F	H	H	H
CH ₃	F	H	H	CH ₃	H	H
CH ₃	F	H	H	F	H	H
CH ₃	F	H	H	H	F	H
CH ₃	F	H	H	H	H	OCH ₃
CH ₃	F	H	H	H	Cl	H
CH ₃	F	H	H	H	OCH ₃	H
Cl	F	H	F	H	F	H
Cl	F	H	F	H	H	H
Cl	F	H	H	CH ₃	H	H
Cl	F	H	H	F	F	H
Cl	F	H	H	F	H	H
Cl	F	H	H	H	Cl	H
Cl	F	H	H	H	F	H
Cl	F	H	H	H	H	OCF ₂ H
Cl	F	H	H	H	H	OCH ₃
F	F	H	F	H	H	H

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F	F	H	H	CH ₃	H	H
F	F	H	H	F	H	H
F	F	H	H	H	F	H
F	F	H	H	H	H	OCH ₃
F	F	H	H	H	Cl	H
F	F	H	H	H	OCH ₃	H
H	F	CF ₃	F	H	H	H
H	F	CF ₃	H	CH ₃	H	H
H	F	CF ₃	H	F	H	H
H	F	CF ₃	H	H	F	H
H	F	CF ₃	H	H	H	OCH ₃
H	F	CF ₃	H	H	Cl	H
H	F	CF ₃	H	H	OCH ₃	H
H	F	CH ₃	F	H	H	H
H	F	CH ₃	H	CH ₃	H	H
H	F	CH ₃	H	F	H	H
H	F	CH ₃	H	H	F	H
H	F	CH ₃	H	H	H	OCH ₃
H	F	CH ₃	H	H	Cl	H
H	F	CH ₃	H	H	OCH ₃	H
H	F	OCF ₂ H	F	H	H	H
H	F	OCF ₂ H	H	CH ₃	H	H
H	F	OCF ₂ H	H	F	H	H
H	F	OCF ₂ H	H	H	F	H
H	F	OCF ₂ H	H	H	H	OCH ₃
H	F	OCF ₂ H	H	H	Cl	H
H	F	OCF ₂ H	H	H	OCH ₃	H
OCF ₂ H	F	H	F	H	H	H
OCF ₂ H	F	H	H	CH ₃	H	H
OCF ₂ H	F	H	H	F	H	H
OCF ₂ H	F	H	H	H	F	H
OCF ₂ H	F	H	H	H	H	OCH ₃
OCF ₂ H	F	H	H	H	Cl	H
OCF ₂ H	F	H	H	H	OCH ₃	H
OCH ₃	F	H	F	H	H	H
OCH ₃	F	H	H	CH ₃	H	H
OCH ₃	F	H	H	F	H	H
OCH ₃	F	H	H	H	F	H
OCH ₃	F	H	H	H	H	OCH ₃
OCH ₃	F	H	H	H	Cl	H
OCH ₃	F	H	H	H	OCH ₃	H

In a further embodiment of the present invention relates

to compounds of (Ic)



selected from the group consisting of compounds of the
 formula (Ia) indicated in Table 13, wherein R_1 , R_{11} , R_{12} ,
 5 R_2^{II} , R_3^{II} , R_4^{II} and R_5^{II} :

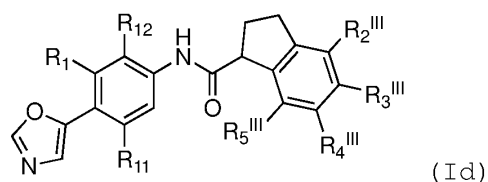
Table 13:						
R_1	R_{11}	R_{12}	R_2^{II}	R_3^{II}	R_4^{II}	R_5^{II}
CF ₃	H	H	F	H	H	H
CF ₃	H	H	H	H	F	H
CF ₃	H	H	H	H	Cl	H
CH ₃	H	H	H	H	F	H
CH ₃	H	H	H	H	Cl	H
Cl	H	H	H	F	F	H
F	H	H	F	H	H	H
F	H	H	H	H	F	H
F	H	H	H	H	Cl	H
OCF ₂ H	H	H	H	H	F	H
OCF ₂ H	H	H	H	H	Cl	H
OCH ₃	H	H	H	H	F	H
OCH ₃	H	H	H	H	Cl	H
H	H	CF ₃	F	H	H	H
H	H	CF ₃	H	H	F	H
H	H	CF ₃	H	H	Cl	H
H	H	CF ₃	H	H	OCH ₃	H
H	H	CH ₃	F	H	H	H
H	H	CH ₃	H	H	F	H
H	H	CH ₃	H	H	Cl	H
H	H	CH ₃	H	H	OCH ₃	H
H	H	OCF ₂ H	F	H	H	H
H	H	OCF ₂ H	H	H	F	H
H	H	OCF ₂ H	H	H	Cl	H
H	H	OCF ₂ H	H	H	OCH ₃	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	F	H	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	CH ₃	H	H

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H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	F	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	F	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	H	OCH ₃
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	Cl	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	OCH ₃	H
CF ₃	F	H	F	H	H	H
CF ₃	F	H	H	CH ₃	H	H
CF ₃	F	H	H	F	H	H
CF ₃	F	H	H	H	F	H
CF ₃	F	H	H	H	H	OCH ₃
CF ₃	F	H	H	H	Cl	H
CF ₃	F	H	H	H	OCH ₃	H
CH ₃	F	H	F	H	H	H
CH ₃	F	H	H	CH ₃	H	H
CH ₃	F	H	H	F	H	H
CH ₃	F	H	H	H	F	H
CH ₃	F	H	H	H	H	OCH ₃
CH ₃	F	H	H	H	Cl	H
CH ₃	F	H	H	H	OCH ₃	H
Cl	F	H	F	H	F	H
Cl	F	H	F	H	H	H
Cl	F	H	H	CH ₃	H	H
Cl	F	H	H	F	F	H
Cl	F	H	H	F	H	H
Cl	F	H	H	H	Cl	H
Cl	F	H	H	H	F	H
Cl	F	H	H	H	H	OCF ₂ H
Cl	F	H	H	H	H	OCH ₃
F	F	H	F	H	H	H
F	F	H	H	CH ₃	H	H
F	F	H	H	F	H	H
F	F	H	H	H	F	H
F	F	H	H	H	H	OCH ₃
F	F	H	H	H	Cl	H
F	F	H	H	H	OCH ₃	H
H	F	CF ₃	F	H	H	H
H	F	CF ₃	H	CH ₃	H	H
H	F	CF ₃	H	F	H	H
H	F	CF ₃	H	H	F	H
H	F	CF ₃	H	H	H	OCH ₃
H	F	CF ₃	H	H	Cl	H
H	F	CF ₃	H	H	OCH ₃	H
H	F	CH ₃	F	H	H	H
H	F	CH ₃	H	CH ₃	H	H
H	F	CH ₃	H	F	H	H
H	F	CH ₃	H	H	F	H
H	F	CH ₃	H	H	H	OCH ₃
H	F	CH ₃	H	H	Cl	H
H	F	CH ₃	H	H	OCH ₃	H

H	F	OCF ₂ H	F	H	H	H
H	F	OCF ₂ H	H	CH ₃	H	H
H	F	OCF ₂ H	H	F	H	H
H	F	OCF ₂ H	H	H	F	H
H	F	OCF ₂ H	H	H	H	OCH ₃
H	F	OCF ₂ H	H	H	Cl	H
H	F	OCF ₂ H	H	H	OCH ₃	H
OCF ₂ H	F	H	F	H	H	H
OCF ₂ H	F	H	H	CH ₃	H	H
OCF ₂ H	F	H	H	F	H	H
OCF ₂ H	F	H	H	H	F	H
OCF ₂ H	F	H	H	H	H	OCH ₃
OCF ₂ H	F	H	H	H	Cl	H
OCF ₂ H	F	H	H	H	OCH ₃	H
OCH ₃	F	H	F	H	H	H
OCH ₃	F	H	H	CH ₃	H	H
OCH ₃	F	H	H	F	H	H
OCH ₃	F	H	H	H	F	H
OCH ₃	F	H	H	H	H	OCH ₃
OCH ₃	F	H	H	H	Cl	H
OCH ₃	F	H	H	H	OCH ₃	H

In a further embodiment of the present invention relates to compounds of (Id)



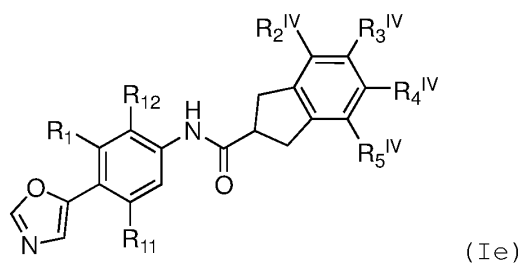
- 5 selected from the group consisting of compounds of the formula (Ia) indicated in Table 14, wherein R₁, R₁₁, R₁₂, R₂^{III}, R₃^{III}, R₄^{III} and R₅^{III}:

Table 14:						
R ₁	R ₁₁	R ₁₂	R ₂ ^{III}	R ₃ ^{III}	R ₄ ^{III}	R ₅ ^{III}
CF ₃	H	H	F	H	H	H
CF ₃	H	H	H	H	F	H
CF ₃	H	H	H	H	Cl	H
CH ₃	H	H	H	H	F	H
CH ₃	H	H	H	H	Cl	H
Cl	H	H	H	F	F	H

F	H	H	F	H	H	H
F	H	H	H	H	F	H
F	H	H	H	H	Cl	H
OCF ₂ H	H	H	H	H	F	H
OCF ₂ H	H	H	H	H	Cl	H
OCH ₃	H	H	H	H	F	H
OCH ₃	H	H	H	H	Cl	H
H	H	CF ₃	F	H	H	H
H	H	CF ₃	H	H	F	H
H	H	CF ₃	H	H	Cl	H
H	H	CF ₃	H	H	OCH ₃	H
H	H	CH ₃	F	H	H	H
H	H	CH ₃	H	H	F	H
H	H	CH ₃	H	H	Cl	H
H	H	CH ₃	H	H	OCH ₃	H
H	H	OCF ₂ H	F	H	H	H
H	H	OCF ₂ H	H	H	F	H
H	H	OCF ₂ H	H	H	Cl	H
H	H	OCF ₂ H	H	H	OCH ₃	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	F	H	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	CH ₃	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	F	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	F	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	H	OCH ₃
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	Cl	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	OCH ₃	H
CF ₃	F	H	F	H	H	H
CF ₃	F	H	H	CH ₃	H	H
CF ₃	F	H	H	F	H	H
CF ₃	F	H	H	H	F	H
CF ₃	F	H	H	H	H	OCH ₃
CF ₃	F	H	H	H	Cl	H
CF ₃	F	H	H	H	OCH ₃	H
CH ₃	F	H	F	H	H	H
CH ₃	F	H	H	CH ₃	H	H
CH ₃	F	H	H	F	H	H
CH ₃	F	H	H	H	F	H
CH ₃	F	H	H	H	H	OCH ₃
CH ₃	F	H	H	H	Cl	H
CH ₃	F	H	H	H	OCH ₃	H
Cl	F	H	F	H	F	H
Cl	F	H	F	H	H	H
Cl	F	H	H	CH ₃	H	H
Cl	F	H	H	F	F	H
Cl	F	H	H	F	H	H
Cl	F	H	H	H	Cl	H
Cl	F	H	H	H	F	H

Cl	F	H	H	H	H	OCF ₂ H
Cl	F	H	H	H	H	OCH ₃
F	F	H	F	H	H	H
F	F	H	H	CH ₃	H	H
F	F	H	H	F	H	H
F	F	H	H	H	F	H
F	F	H	H	H	H	OCH ₃
F	F	H	H	H	Cl	H
F	F	H	H	H	OCH ₃	H
H	F	CF ₃	F	H	H	H
H	F	CF ₃	H	CH ₃	H	H
H	F	CF ₃	H	F	H	H
H	F	CF ₃	H	H	F	H
H	F	CF ₃	H	H	H	OCH ₃
H	F	CF ₃	H	H	Cl	H
H	F	CF ₃	H	H	OCH ₃	H
H	F	CH ₃	F	H	H	H
H	F	CH ₃	H	CH ₃	H	H
H	F	CH ₃	H	F	H	H
H	F	CH ₃	H	H	F	H
H	F	CH ₃	H	H	H	OCH ₃
H	F	CH ₃	H	H	Cl	H
H	F	CH ₃	H	H	OCH ₃	H
H	F	OCF ₂ H	F	H	H	H
H	F	OCF ₂ H	H	CH ₃	H	H
H	F	OCF ₂ H	H	F	H	H
H	F	OCF ₂ H	H	H	F	H
H	F	OCF ₂ H	H	H	H	OCH ₃
H	F	OCF ₂ H	H	H	Cl	H
H	F	OCF ₂ H	H	H	OCH ₃	H
OCF ₂ H	F	H	F	H	H	H
OCF ₂ H	F	H	H	CH ₃	H	H
OCF ₂ H	F	H	H	F	H	H
OCF ₂ H	F	H	H	H	F	H
OCF ₂ H	F	H	H	H	H	OCH ₃
OCF ₂ H	F	H	H	H	Cl	H
OCF ₂ H	F	H	H	H	OCH ₃	H
OCH ₃	F	H	F	H	H	H
OCH ₃	F	H	H	CH ₃	H	H
OCH ₃	F	H	H	F	H	H
OCH ₃	F	H	H	H	F	H
OCH ₃	F	H	H	H	H	OCH ₃
OCH ₃	F	H	H	H	Cl	H
OCH ₃	F	H	H	H	OCH ₃	H

In a further embodiment of the present invention relates to compounds of (Ie)



selected from the group consisting of compounds of the formula (Ie) indicated in Table 15, wherein R_1 , R_{11} , R_{12} , R_2^{IV} , R_3^{IV} , R_4^{IV} and R_5^{IV} :

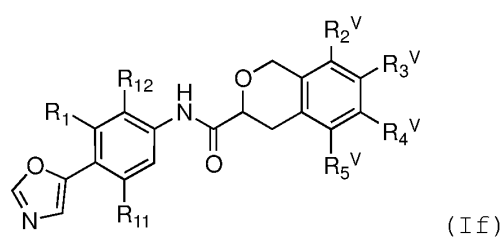
Table 15:						
R_1	R_{11}	R_{12}	R_2^{IV}	R_3^{IV}	R_4^{IV}	R_5^{IV}
CF ₃	H	H	F	H	H	H
CF ₃	H	H	H	H	F	H
CF ₃	H	H	H	H	Cl	H
CH ₃	H	H	H	H	F	H
CH ₃	H	H	H	H	Cl	H
Cl	H	H	H	F	F	H
F	H	H	F	H	H	H
F	H	H	H	H	F	H
F	H	H	H	H	Cl	H
OCF ₂ H	H	H	H	H	F	H
OCF ₂ H	H	H	H	H	Cl	H
OCH ₃	H	H	H	H	F	H
OCH ₃	H	H	H	H	Cl	H
H	H	CF ₃	F	H	H	H
H	H	CF ₃	H	H	F	H
H	H	CF ₃	H	H	Cl	H
H	H	CF ₃	H	H	OCH ₃	H
H	H	CH ₃	F	H	H	H
H	H	CH ₃	H	H	F	H
H	H	CH ₃	H	H	Cl	H
H	H	CH ₃	H	H	OCH ₃	H
H	H	OCF ₂ H	F	H	H	H
H	H	OCF ₂ H	H	H	F	H
H	H	OCF ₂ H	H	H	Cl	H
H	H	OCF ₂ H	H	H	OCH ₃	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	F	H	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	CH ₃	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	F	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	F	H

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H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	H	OCH ₃
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	Cl	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	OCH ₃	H
CF ₃	F	H	F	H	H	H
CF ₃	F	H	H	CH ₃	H	H
CF ₃	F	H	H	F	H	H
CF ₃	F	H	H	H	F	H
CF ₃	F	H	H	H	H	OCH ₃
CF ₃	F	H	H	H	Cl	H
CF ₃	F	H	H	H	OCH ₃	H
CH ₃	F	H	F	H	H	H
CH ₃	F	H	H	CH ₃	H	H
CH ₃	F	H	H	F	H	H
CH ₃	F	H	H	H	F	H
CH ₃	F	H	H	H	H	OCH ₃
CH ₃	F	H	H	H	Cl	H
CH ₃	F	H	H	H	OCH ₃	H
Cl	F	H	F	H	F	H
Cl	F	H	F	H	H	H
Cl	F	H	H	CH ₃	H	H
Cl	F	H	H	F	F	H
Cl	F	H	H	F	H	H
Cl	F	H	H	H	Cl	H
Cl	F	H	H	H	F	H
Cl	F	H	H	H	H	OCF ₂ H
Cl	F	H	H	H	H	OCH ₃
F	F	H	F	H	H	H
F	F	H	H	CH ₃	H	H
F	F	H	H	F	H	H
F	F	H	H	H	F	H
F	F	H	H	H	H	OCH ₃
F	F	H	H	H	Cl	H
F	F	H	H	H	OCH ₃	H
H	F	CF ₃	F	H	H	H
H	F	CF ₃	H	CH ₃	H	H
H	F	CF ₃	H	F	H	H
H	F	CF ₃	H	H	F	H
H	F	CF ₃	H	H	H	OCH ₃
H	F	CF ₃	H	H	Cl	H
H	F	CF ₃	H	H	OCH ₃	H
H	F	CH ₃	F	H	H	H
H	F	CH ₃	H	CH ₃	H	H
H	F	CH ₃	H	F	H	H
H	F	CH ₃	H	H	F	H
H	F	CH ₃	H	H	H	OCH ₃
H	F	CH ₃	H	H	Cl	H
H	F	CH ₃	H	H	OCH ₃	H
H	F	OCF ₂ H	F	H	H	H
H	F	OCF ₂ H	H	CH ₃	H	H

H	F	OCF ₂ H	H	F	H	H
H	F	OCF ₂ H	H	H	F	H
H	F	OCF ₂ H	H	H	H	OCH ₃
H	F	OCF ₂ H	H	H	Cl	H
H	F	OCF ₂ H	H	H	OCH ₃	H
OCF ₂ H	F	H	F	H	H	H
OCF ₂ H	F	H	H	CH ₃	H	H
OCF ₂ H	F	H	H	F	H	H
OCF ₂ H	F	H	H	H	F	H
OCF ₂ H	F	H	H	H	H	OCH ₃
OCF ₂ H	F	H	H	H	Cl	H
OCF ₂ H	F	H	H	H	OCH ₃	H
OCH ₃	F	H	F	H	H	H
OCH ₃	F	H	H	CH ₃	H	H
OCH ₃	F	H	H	F	H	H
OCH ₃	F	H	H	H	F	H
OCH ₃	F	H	H	H	H	OCH ₃
OCH ₃	F	H	H	H	Cl	H
OCH ₃	F	H	H	H	OCH ₃	H

In a further embodiment of the present invention relates to compounds of (If)



- 5 selected from the group consisting of compounds of the formula (If) indicated in Table 16, wherein R₁, R₁₁, R₁₂, R₂^V, R₃^V, R₄^V and R₅^V:

Table 16:						
R ₁	R ₁₁	R ₁₂	R ₂ ^V	R ₃ ^V	R ₄ ^V	R ₅ ^V
CF ₃	H	H	F	H	H	H
CF ₃	H	H	H	H	F	H
CF ₃	H	H	H	H	Cl	H
CH ₃	H	H	H	H	F	H
CH ₃	H	H	H	H	Cl	H
Cl	H	H	H	F	F	H

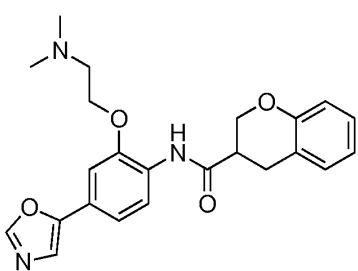
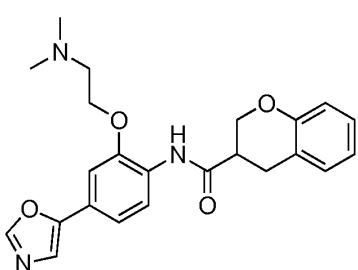
F	H	H	F	H	H	H
F	H	H	H	H	F	H
F	H	H	H	H	Cl	H
OCF ₂ H	H	H	H	H	F	H
OCF ₂ H	H	H	H	H	Cl	H
OCH ₃	H	H	H	H	F	H
OCH ₃	H	H	H	H	Cl	H
H	H	CF ₃	F	H	H	H
H	H	CF ₃	H	H	F	H
H	H	CF ₃	H	H	Cl	H
H	H	CF ₃	H	H	OCH ₃	H
H	H	CH ₃	F	H	H	H
H	H	CH ₃	H	H	F	H
H	H	CH ₃	H	H	Cl	H
H	H	CH ₃	H	H	OCH ₃	H
H	H	OCF ₂ H	F	H	H	H
H	H	OCF ₂ H	H	H	F	H
H	H	OCF ₂ H	H	H	Cl	H
H	H	OCF ₂ H	H	H	OCH ₃	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	F	H	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	CH ₃	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	F	H	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	F	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	H	OCH ₃
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	Cl	H
H	H	OCH ₂ CH ₂ N(CH ₃) ₂	H	H	OCH ₃	H
CF ₃	F	H	F	H	H	H
CF ₃	F	H	H	CH ₃	H	H
CF ₃	F	H	H	F	H	H
CF ₃	F	H	H	H	F	H
CF ₃	F	H	H	H	H	OCH ₃
CF ₃	F	H	H	H	Cl	H
CF ₃	F	H	H	H	OCH ₃	H
CH ₃	F	H	F	H	H	H
CH ₃	F	H	H	CH ₃	H	H
CH ₃	F	H	H	F	H	H
CH ₃	F	H	H	H	F	H
CH ₃	F	H	H	H	H	OCH ₃
CH ₃	F	H	H	H	Cl	H
CH ₃	F	H	H	H	OCH ₃	H
Cl	F	H	F	H	F	H
Cl	F	H	F	H	H	H
Cl	F	H	H	CH ₃	H	H
Cl	F	H	H	F	F	H
Cl	F	H	H	F	H	H
Cl	F	H	H	H	Cl	H
Cl	F	H	H	H	F	H

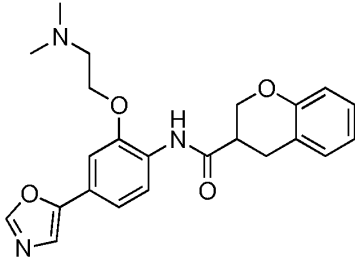
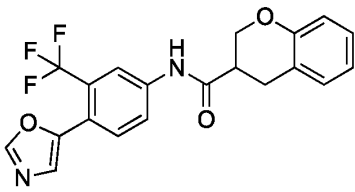
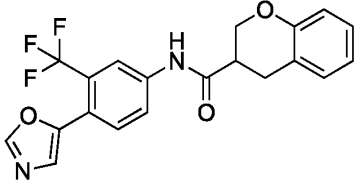
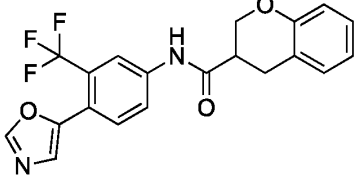
Cl	F	H	H	H	H	OCF ₂ H
Cl	F	H	H	H	H	OCH ₃
F	F	H	F	H	H	H
F	F	H	H	CH ₃	H	H
F	F	H	H	F	H	H
F	F	H	H	H	F	H
F	F	H	H	H	H	OCH ₃
F	F	H	H	H	Cl	H
F	F	H	H	H	OCH ₃	H
H	F	CF ₃	F	H	H	H
H	F	CF ₃	H	CH ₃	H	H
H	F	CF ₃	H	F	H	H
H	F	CF ₃	H	H	F	H
H	F	CF ₃	H	H	H	OCH ₃
H	F	CF ₃	H	H	Cl	H
H	F	CF ₃	H	H	OCH ₃	H
H	F	CH ₃	F	H	H	H
H	F	CH ₃	H	CH ₃	H	H
H	F	CH ₃	H	F	H	H
H	F	CH ₃	H	H	F	H
H	F	CH ₃	H	H	H	OCH ₃
H	F	CH ₃	H	H	Cl	H
H	F	CH ₃	H	H	OCH ₃	H
H	F	OCF ₂ H	F	H	H	H
H	F	OCF ₂ H	H	CH ₃	H	H
H	F	OCF ₂ H	H	F	H	H
H	F	OCF ₂ H	H	H	F	H
H	F	OCF ₂ H	H	H	H	OCH ₃
H	F	OCF ₂ H	H	H	Cl	H
H	F	OCF ₂ H	H	H	OCH ₃	H
OCF ₂ H	F	H	F	H	H	H
OCF ₂ H	F	H	H	CH ₃	H	H
OCF ₂ H	F	H	H	F	H	H
OCF ₂ H	F	H	H	H	F	H
OCF ₂ H	F	H	H	H	H	OCH ₃
OCF ₂ H	F	H	H	H	Cl	H
OCF ₂ H	F	H	H	H	OCH ₃	H
OCH ₃	F	H	F	H	H	H
OCH ₃	F	H	H	CH ₃	H	H
OCH ₃	F	H	H	F	H	H
OCH ₃	F	H	H	H	F	H
OCH ₃	F	H	H	H	H	OCH ₃
OCH ₃	F	H	H	H	Cl	H
OCH ₃	F	H	H	H	OCH ₃	H

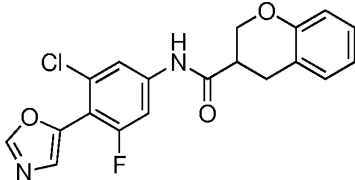
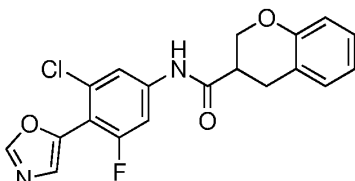
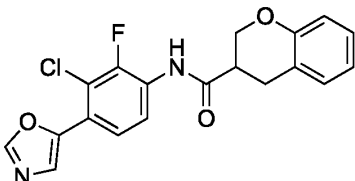
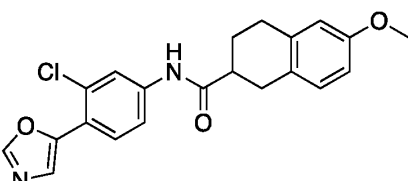
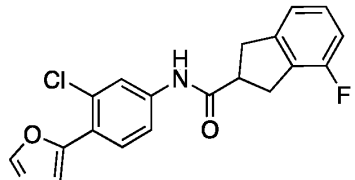
As already mentioned, it could be shown that the compounds according to the present invention and the compositions

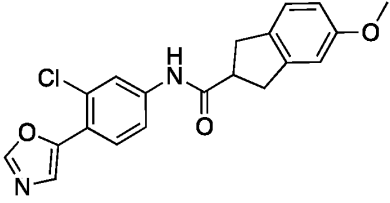
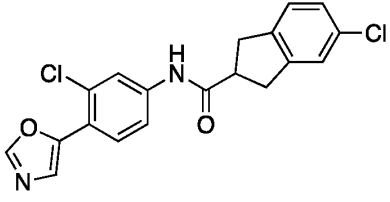
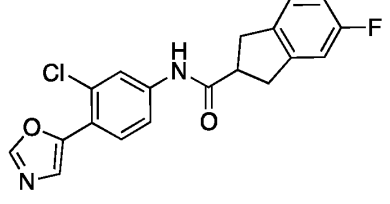
according to the present invention stimulate the proliferation and/or differentiation of RPE cells. Thus, they are suitable in the treatment and/or prevention of RPE-related diseases, in particular of RPE diseases from the family of macular degeneration leading to loss of vision.

Especially good results could be obtained by the following compounds according to the present invention:

Table 17:	
Comp. No.	Chemical structure
34	 (racemate)
35	 enantiomer with the shorter retention time from the chiral HPLC resolution

36	 enantiomer with the longer retention time from the chiral HPLC resolution
37	 (racemate)
38	 enantiomer with the shorter retention time from the chiral HPLC resolution
39	 enantiomer with the longer retention time from the chiral HPLC resolution

40	 enantiomer with the shorter retention time from the chiral HPLC resolution
41	 enantiomer with the longer retention time from the chiral HPLC resolution
42	 (racemate)
43	 (racemate)
44	

	(racemate)
45	 (racemate)
46	 (racemate)
47	 (racemate)

In a preferred embodiment of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier and/or adjuvant; and a compound of the formula (I) as defined above, preferably a compound of formula (Ia), (Ib), (Ic), (Id), (Ie) or (If). Most preferably, it comprises a compound of formula (Ia), (Ib), (Ic), (Id), (Ie) or (If) as disclosed in Table 11, Table 12, Table 13, Table 14, Table 15, Table 16, and Table 17 above.

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Experimental Section

Cell culture

Induced pluripotent stem cell-derived fetal RPE (iPSC-frPE) cells acquired from the University of California, Santa Barbara, were generated from human fetal RPE cells that were isolated and reprogramed to iPSC, then differentiated and sorted for cellular markers to collect RPE progenitors. Vials were transported frozen on dry ice and stored in minus 80°C.

For the phenotypic screens, iPSC-frPE cells were thawed and cultured in Matrigel-coated flasks with N1VA media containing 1XMEM solution supplemented with 2.2g/L Sodium Bicarbonate, 0.25mg/ml Taurine, 0.02ug/ml Hydrocortisone, 0.013ug/ml Triiodo Thyronine, 0.1ug/ml Lipoic acid, 1% MEM Non-Essential Amino Acids, 1% Penicilin/Streptomycin, 2% Neurocult SM1 supplement and 1% N1 supplement. For the initial cultures, Thiazovivin was added to the media at 2uM for the first 24hr of incubation, after which the media was replaced with fresh N1VA media for additional three-day incubation at 37°C with 5% CO₂.

Compound screens

iPSC-frPE cells were plated with N1VA media at a density of 10,000 cells per well in Matrigel-coated 96-well plates and cultured for 24hr prior to the treatment with test compounds at a final concentration of 5µM in 0.1% DMSO. Internal controls for each test plate were (a) 0.1% DMSO as a negative control and (b) 0.1% DMSO + 10ng/ml human recombinant bFGF (STEMCELL) as a positive control. To

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identify hits that promote RPE pigmentation, cells were maintained for a period of 32 days and treated with medium containing the test or control compounds according to the media exchange regimen (Fig. 1). The degree of pigmentation was quantified by measuring the light absorbance at 510nm with Cytation5 imaging reader (BIOTEK). Compounds that increased the normalized absorbance endpoint by more than three standard deviations over the average DMSO readout per plate were considered as hits. Pigmentation values are finally reported relative to plate internal DMSO controls.

Preparation of the compounds of the invention

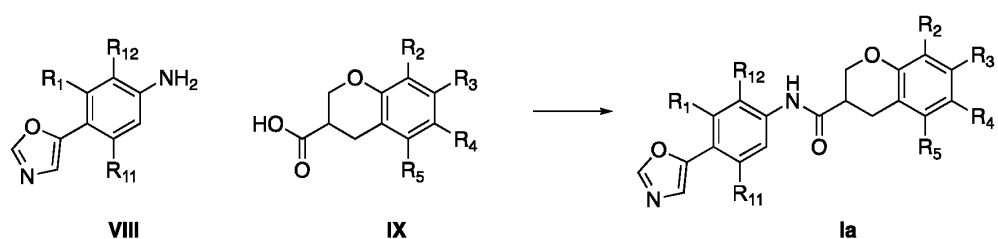
The compounds of formula (I) may be prepared by methods described below, together with synthetic methods known in the art of organic chemistry, or modifications that are familiar to those of ordinary skill in the art. The starting materials used herein are available commercially or may be prepared by routine methods known in the art, such as those methods described in standard reference books such as "Compendium of Organic Synthetic Methods, Vol. I-XlN" (published with Wiley-Interscience, ISSN: 1934-4783). Preferred methods include, but are not limited to, those described below.

The schemes are representative of methods useful in synthesizing the compounds of the present invention and the supporting examples. They are not to constrain the scope of the invention in anyway.

General methods - Synthesis

Method 1:

Scheme 1:

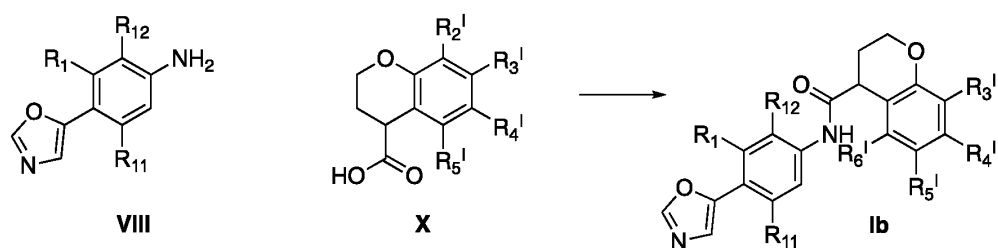


where R₁, R₁₁, R₁₂, R₂, R₃, R₄ and R₅ are as described in
 5 formula I.

Compounds of general formula Ia (Scheme 1) may be prepared by reacting compounds of general formula VIII with a carboxylic acid of general formula IX using procedures known to chemists skilled in the art.

10 Method 2

Scheme 2:



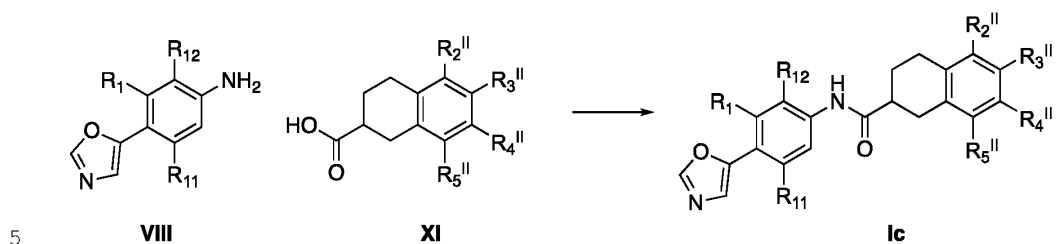
Where R₁, R₁₁, R₁₂, R₂^I, R₃^I, R₄^I and R₅^I are as described in
 formula I.

15 Compounds of general formula Ib (Scheme 2) may be prepared by reacting compounds of general formula VIII with a

carboxylic acid of general formula X using procedures known to chemists skilled in the art.

Method 3:

Scheme 3:

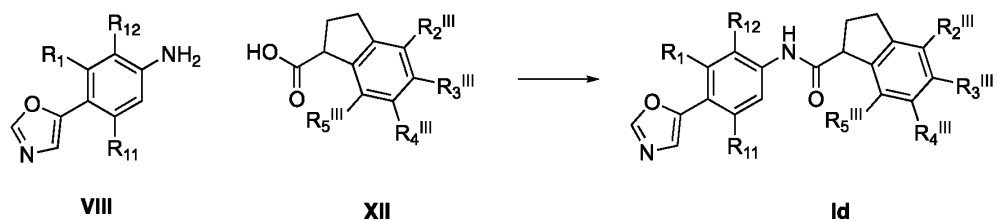


where R_1 , R_{11} , R_{12} , R_2^{II} , R_3^{II} , R_4^{II} and R_5^{II} are as described in formula I.

Compounds of general formula Ic (Scheme 3) may be prepared by reacting compounds of general formula VIII with a
10 carboxylic acid of general formula XI using procedures known to chemists skilled in the art.

Method 4:

Scheme 4:

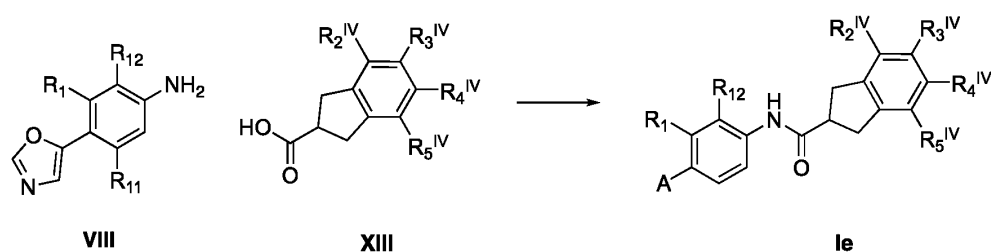


15 where R_1 , R_{11} , R_{12} , R_2^{III} , R_3^{III} , R_4^{III} and R_5^{III} are as described in formula I.

Compounds of general formula Id (Scheme 4) may be prepared by reacting compounds of general formula VIII with a carboxylic acid of general formula XII using procedures known to chemists skilled in the art.

5 Method 5:

Scheme 5:

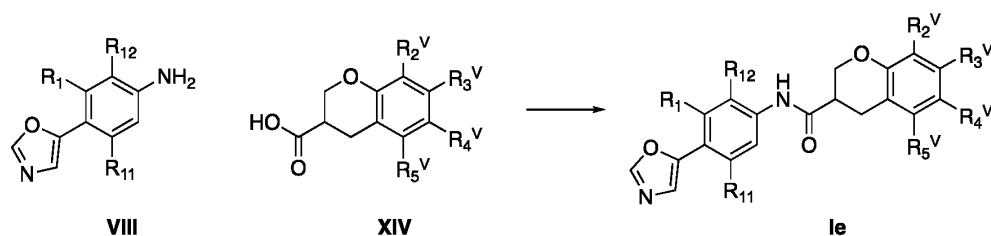


where R₁, R₁₁, R₁₂, R₂^{IV}, R₃^{IV}, R₄^{IV} and R₅^{IV} are as described in formula I.

10 Compounds of general formula Id (Scheme 5) may be prepared by reacting compounds of general formula VIII with a carboxylic acid of general formula XIII using procedures known to chemists skilled in the art.

Method 6:

15 Scheme 6:



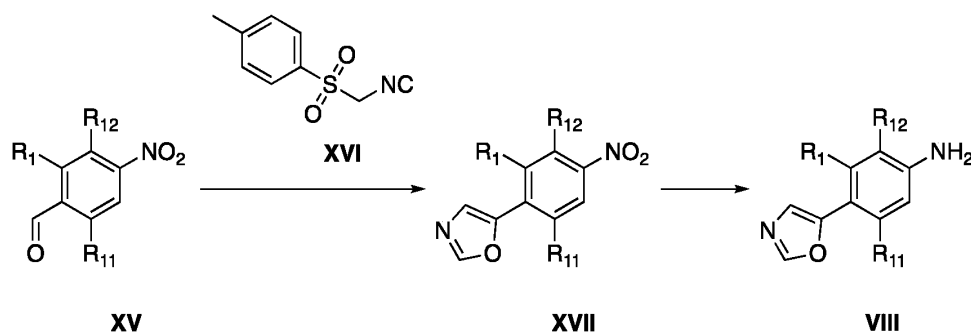
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where R_1 , R_{11} , R_{12} , R_2^V , R_3^V , R_4^V and R_5^V are as described in formula I.

Compounds of general formula Ie (Scheme 6) may be prepared by reacting compounds of general formula VIII with a
 5 carboxylic acid of general formula XIV using procedures known to chemists skilled in the art.

Method 7:

Scheme 7:



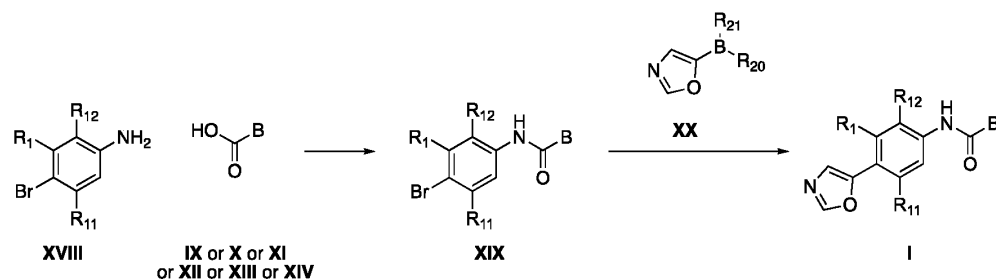
10 where R_1 , R_{12} and R_{11} are as described in formula I.

Compounds of general formula VIII (Scheme 7) may be prepared by reduction of the nitro group in compounds of general formula XVII using procedures known to chemists skilled in the art. Compounds of general formula XVII may
 15 be prepared from aldehydes of general formula XV by reaction in the presence of a reagent such as tosylmethyl isocyanide (XVI) in the presence of a base such as potassium carbonate.

Method 8:

20 Scheme 8:

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where R_1 , R_{11} and R_{12} are as described in formula I, R_{20} and R_{21} are both hydroxy groups or form together with the boron atom a 4,4,5,5-tetramethyl-1,3,2-dioxaborolane group.

5 Compounds of general formula I (Scheme 8) may be prepared from compounds of general formulae XIX and XX in the presence of a palladium catalyst such as tetrakis(triphenylphosphin)palladium(0) and a base such as potassium carbonate or other Suzuki-Miyaura coupling
 10 reaction conditions known to chemists skilled in the art of organic synthesis. Compounds of general formula XIX may be prepared by reacting compounds of general formula from XVIII with a carboxylic acid of general formula IX-XIV using procedures known to chemists skilled in the art.

15 Analytic Methods

^1H NMR spectra were recorded in $\text{DMSO}-d_6$ / CD_3OD / CDCl_3 solution in 5mm o.d. tubes [Wilmad NMR tubes (Sigma-Aldrich), 5mm Thin Wall, 7" Length] at 300.0 K and were collected on Bruker Avance NMRS-400 at 400 MHz for ^1H . The
 20 chemical shifts (δ) are relative to CDCl_3 ($\text{CDCl}_3 = 7.26$ ppm), $\text{DMSO}-d_6$ ($\text{DMSO}-d_6 = 2.5$ ppm), CD_3OD ($\text{CD}_3\text{OD} = 3.3$ ppm) and expressed in ppm. The chemical shifts in CDCl_3 , $\text{DMSO}-d_6$ and CD_3OD are relative to tetramethylsilane (TMS, = 0.00 ppm) and expressed in ppm.

Analytical HPLC

Analytical HPLC Method A: Chromegabond WR C18 (3 cm x 3.2 mm, 3 μ) column operated with a flow rate of 1.5 mL/min. As mobile phases, 0.02% TFA in water (mobile phase C) and
5 0.02% TFA in CH₃CN (mobile phase D) were used in a gradient starting at 90% C and 10% D, changed to 10% C and 90% D in 3.0 min, then to 90% C and 10% D in 4.0 min, which was held constant up to 5.1 min.

Analytical HPLC Method B: Restek Ultra AQ C18 (30 x 2.1
10 mm, 3 μ) column operated with a flow rate of 1.5 mL/min. As mobile phases, 0.05% HCOOH in water (mobile phase A) and CH₃CN (mobile phase B) were used in a gradient starting at 98% A and 2% B held for 0.75 min, then to 90% A and 10% B in 1.5 min, further to 2% A and 98% B in 3.0 min, held
15 this mobile phase composition up to 4.0 min and finally back to initial condition at 5.0 min.

Analytical HPLC Method C: Column-YMC TRIART C18 (33 x 2.1 mm, 3 μ), (mobile phase: 95% [0.01% HCOOH in water] and 5% [0.01% HCOOH in CH₃CN] held for 0.50min then to 99%
20 [0.01% HCOOH in water] and 1% [0.01% HCOOH in CH₃CN] in 3.0 min, held this mobile phase composition up to 4.0 min, and finally back to initial condition in 4.10 min, held this mobile phase composition up to 4.50 min). Flow =1.0 ml/min.

25 Preparative HPLC

Preparative HPLC Method A: Waters Sunfire C18 OBD Prep Column, 100 A, 5 μ m, 19 mm x 100 mm with SunFire C18 Prep Guard Cartridge, 100 A, 10 μ m, 19 mm x 10 mm was used.

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Deionized Water (phase A) and HPLC-grade Methanol (phase B) were used as an eluent.

Preparative HPLC Method B: Waters auto purification instrument with a YMC Triart C18 (250 x 21.2 mm, 5µ)
5 column operated at room temperature with a flow rate of 16 mL/min. Samples were eluted with 20 mM ammonium bicarbonate in water (mobile phase A) and acetonitrile (mobile phase B) and a gradient profile of 70% A and 30% B initially, then 45% A and 55% B in 3 min, adapted to 20% A
10 and 80% B in 20 min, then to 5% A and 95% B in 21 min, which was held constant for 2 min. Pure fractions were concentrated to yield the final product.

Methods for chiral separation

Chiral Analytical Methods

15 Chiral Separation Method A: Separation was accomplished using Agilent Prep-HPLC, Column: Regis Reflect C-Amylose A containing Amylose tris(3,5-dimethylphenylcarbamate) (250 x 30 mm, 5µ), Flow: 35 g/min, Mobile Phase: 35 % CO₂ + 65 % (0.1% NH₃ in MeOH), ABPR: 100 bar, Temperature: 35° C.

20 Chiral Separation Method B: Separation was accomplished using Agilent Prep-HPLC, Column: Daicel Chiralpak IG (250x20 mm) containing tris(3-chloro-5 methylphenylcarbamate) substituted amylose immobilized on 5µm silica; Flow: 25 g/min, Mobile Phase: 45 % CO₂ + 55 %
25 (0.1% NH₃ in MeOH), ABPR: 120 bar, Temperature: 35°C.

Chiral Separation Method C: Separation was accomplished using: Column: Regis Reflect C-Amylose A containing Amylose tris(3,5-dimethylphenylcarbamate) (250 x 30 mm, 5

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μ), Mobile phase: 40 %CO₂ + 60 % (0.1% ammonia in MeOH),
Flow rate: 25.0 g/min, Run time: 10 min, Wave length: 220
nm, ABPR: 110 bar, Temperature: 35 °C.

Chiral Separation Method D: Separation was accomplished
5 using Agilent Prep-HPLC, Column: Chiralpak IG (250 x 30
mm, 5μ), Flow: 35 g/min, Mobile Phase: 35 % CO₂ + 65 %
(0.1% NH₃ in MeOH), ABPR: 100 bar, Temperature: 35° C.

Chiral Separation Method E: Separation was accomplished
using Agilent Prep-HPLC, Column: Chiralpak IG (250 x 30
10 mm, 5μ), Flow: 25 g/min, Mobile Phase: 60 % CO₂ + 40 %
(0.1% NH₃ in MeOH), ABPR: 100 bar, Temperature: 35° C.

Chiral Separation Method F: Separation was accomplished
using Agilent Prep-HPLC, Column: Chiralpak IG (250 x 30
mm, 5μ), Flow: 25 g/min, Mobile Phase: 45 % CO₂ + 55 %
15 (0.1% NH₃ in MeOH), ABPR: 120 bar, Temperature: 35° C.

Chiral Separation Method G: Separation was accomplished
using column: Chiralpak AD-H (4.6 x 250 mm, 5μ); Mobile
Phase: 100% EtOH; Flow Rate: 0.5 ml/min; Column
Temperature: 24°C; Wavelength: 286 nm.

20 Chiral Preparative Methods

Chiral Separation Method H: performed using a Daicel
Chiralpak AD-H (250 × 20 mm × 5 μm) column coated with
amylose-tris(3,5-dimethylphenylcarbamate); Mobile phase:
Hexane-IPA-MeOH, 70-15-15 Flow Rate: 12 mL/min; Column
25 Temperature: 24°C; Wavelength: 210 nm, 225 nm, 254nm.

Chiral Separation Method I: performed using a Daicel
Chiralpak AD-H (250 × 20 mm × 5 μm) column coated with

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amylose-tris(3,5-dimethylphenylcarbamate); Mobile phase: Hexane-IPA-MeOH, 70-15-15 Flow Rate: 12 mL/min; Column Temperature: 24°C; Wavelength: 215 nm, 280 nm.

Chiral Separation Method K: performed using a Daicel
5 Chiralpak AD-H (250 × 20 mm × 5 µm) column coated with amylose-tris(3,5-dimethylphenylcarbamate); Mobile phase: EtOH, Flow Rate: 10 mL/min; Column Temperature: 24°C; Wavelength: 286 nm.

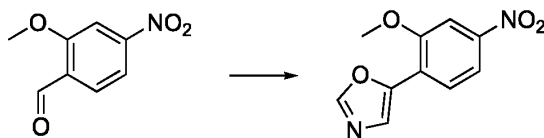
General synthetic procedures

10 Coupling procedure A: the carboxylic acid (1.1 mmol) and a solution of *N*-hydroxybenzotriazole in DMSO (100 g/L, 2 mL, 1.5 mmol) were placed in a vial, and the aniline derivative (1 mmol) was added. If amine was used as a hydrochloride, Et₃N (1 mmol) was also added. The reaction
15 mixture was stirred for 30 min in a shaker, and EDC (1.2 mmol) was added. After all the reagents were loaded, the vial was sealed and stirred in a shaker for 1 h. If clear solution was formed, the vial was left at room temperature for 24 h. Otherwise, the reaction mixture was kept in a
20 sonication bath for 24 h (strong heating should be avoided). If strong thickening of the reaction mixture was observed so that stirring was not effective, 0.2 mL of DMSO might be added in one portion. The crude reaction mixture was analyzed by LC-MS and then subjected to
25 chromatographic purification. The purification was performed using Agilent 1260 Infinity systems equipped with DAD and mass-detector.

Synthesis of intermediates

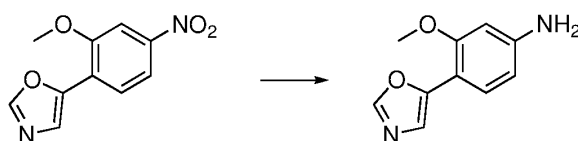
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Preparation of 5-(2-methoxy-4-nitrophenyl)oxazole



To a stirred solution of 2-methoxy-4-nitrobenzaldehyde (3.00 g, 16.6 mmol) in methanol (20 mL) was added 1-(isocyanomethane)sulfonyl-4-methylbenzene (3.80 g, 19.9 mmol) followed by K_2CO_3 (8.00 g, 58.0 mmol) and the reaction mixture was heated to 80°C for 2 h. After completion of the reaction, reaction mass was poured into sat $NaHCO_3$ solution (20 mL) and extracted into ethyl acetate (3 x 100 mL). The organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to get a crude which was purified by flash silica gel chromatography (eluted at 30% ethyl acetate in hexane) to get 5-(2-methoxy-4-nitrophenyl)-1,3-oxazole (2.1 g, 57 %). LCMS: 221 (M+H).

Preparation of 3-methoxy-4-(1,3-oxazol-5-yl)aniline

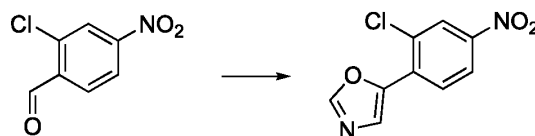


To a stirred solution of 5-(2-methoxy-4-nitrophenyl)-1,3-oxazole (1.00 g, 4.52 mmol) in ethanol (20 mL) were added tin(II) chloride (5.14 g, 27.1 mmol) and conc. HCl (6 mL) solution drop wise at 0°C and then stirred for 6h at room temperature. After completion of the reaction, the reaction mixture was diluted with sat. $NaHCO_3$ solution (20 mL), extracted with ethyl acetate (3 x 200 mL) and the

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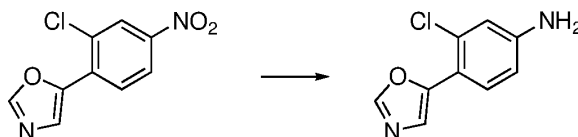
organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to get crude of 3-methoxy-4-(1,3-oxazol-5-yl)aniline (700 mg, 81%). LCMS: 191 (M+H).

5 Preparation of 5-(2-chloro-4-nitrophenyl)-1,3-oxazole



To a stirred solution of 2-chloro-4-nitrobenzaldehyde (3 g, 16.16 mmol) and 1-(isocyanomethane)sulfonyl-4-methylbenzene (4.1 g, 21.0 mmol) in MeOH (30mL) was added
10 K_2CO_3 (8.9 g, 64.66 mmol) and the reaction mixture was heated to 80°C for 2 h. After completion of the reaction, the reaction mass was poured into saturated $NaHCO_3$ solution (20 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with water, brine, dried
15 over anhydrous sodium sulphate and concentrated under vacuum to get a crude which was purified by flash silica gel chromatography (eluted with 30% ethyl acetate in hexane) to afford 5-(2-chloro-4-nitrophenyl)-1,3-oxazole (2.1 g, 57%). LCMS: 225.2 (M+H).

20 Preparation of 3-chloro-4-(1,3-oxazol-5-yl)aniline

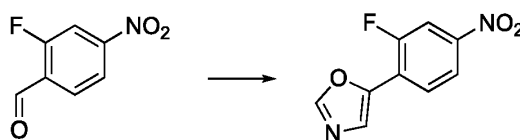


To a stirred solution of 5-(2-chloro-4-nitrophenyl)-1,3-oxazole (3 g, 13.4 mmol) in EtOH (40 mL) were added

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tin(II) chloride dihydrate (12.08 g, 53.57 mmol) and conc. HCl (5 mL) dropwise at 0°C and the reaction mixture was stirred for 30 min at 80°C. After completion of the reaction, the reaction mass was neutralized using a 2N NaOH solution and extracted with ethyl acetate (2 x 50 mL). The organic layer was thoroughly washed with water, dried over anhydrous sodium sulphate and concentrated under vacuum to afford 3-chloro-4-(1,3-oxazol-5-yl)aniline (1.5 g, 57%). LCMS: 195 (M+H).

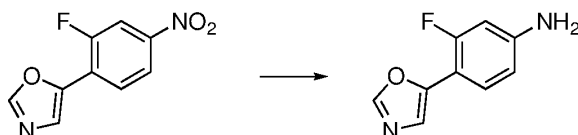
10 Preparation of 5-(2-fluoro-4-nitrophenyl)-1,3-oxazole



To a stirred solution of 2-fluoro-4-nitro benzaldehyde (5 g, 29.56 mmol) and 1-(isocyanomethane)sulfonyl-4-methylbenzene (7.5 g, 38.43 mmol) in MeOH (35 mL) was added K₂CO₃ (16.3 g, 118.27 mmol) and the reaction mixture was heated to 80°C for 2 h. After completion of the reaction, reaction mass was poured into saturated NaHCO₃ solution (50 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to get a crude which was purified by flash silica gel chromatography (eluted with 30% ethyl acetate in hexane) to afford 5-(2-fluoro-4-nitrophenyl)-1,3-oxazole (2.5 g, 40%). LCMS: 209.2 (M+H).

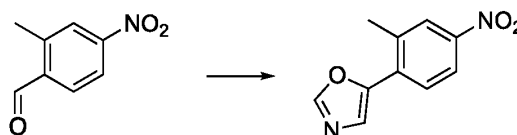
25 Preparation of 3-fluoro-4-(1,3-oxazol-5-yl)aniline

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To a stirred solution of 5-(2-fluoro-4-nitrophenyl)-1,3-oxazole (700 mg, 3.36 mmol) in EtOH (35 mL) were added tin(II) chloride dihydrate (3.03 g, 13.46 mmol) and conc. HCl (2 mL) dropwise at 0°C and the reaction mixture was stirred for 30 min at 80°C. After completion of the reaction, the reaction mass was neutralized with a 2N NaOH solution and extracted with ethyl acetate (2 x 50 mL). The organic layer was thoroughly washed with water, dried over anhydrous sodium sulphate and concentrated under vacuum to afford 3-fluoro-4-(1,3-oxazol-5-yl)aniline (350 mg, 53%). LCMS: 179 (M+H).

Preparation of 5-(2-methyl-4-nitrophenyl)oxazole

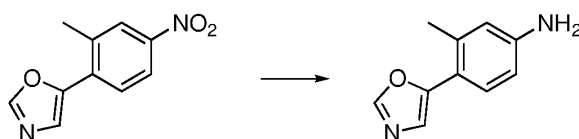


To a stirred solution of 2-methyl-4-nitrobenzaldehyde (1.02 g, 6.05 mmol) and 1-(isocyanomethane)sulfonyl-4-methylbenzene (1.36 g, 7.05 mmol) in MeOH (25 mL) was added potassium carbonate (1.67 g, 12.1 mmol) and the reaction mixture was heated to reflux for 2 h. After consumption of starting material by TLC, the reaction mixture was cooled to room temperature, the solvent was evaporated under reduced pressure, the residue was treated with saturated aqueous solution of NaHCO₃ (20 mL), and extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with water (30 mL), brine (20 mL), dried

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over anhydrous Na_2SO_4 , and concentrated under reduced pressure to get crude which was purified by flash column chromatography to get 5-(2-methyl-4-nitrophenyl)oxazole (1.2 g, 91%).

5 Preparation of 3-methyl-4-(oxazol-5-yl)aniline



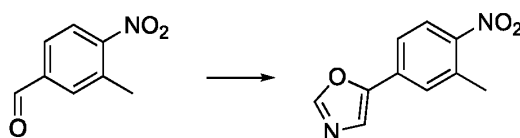
To a stirred solution of 5-(2-methyl-4-nitrophenyl)oxazole (1.1 g, 5.39 mmol) in ethanol (20 mL) was added tin(II) chloride dihydrate (4.08 g, 21.5 mmol) at room temperature.

10 The mixture was cooled to 0°C and conc. HCl (3.0 mL) was added drop wise. The reaction mixture was then stirred for 0.5 h at 80°C . After completion of the reaction by TLC, the reaction mixture was cooled to room temperature, diluted with saturated aqueous solution of NaHCO_3 solution

15 (30 mL), and extracted with ethyl acetate (3 x 30 mL). Organic layers were combined, washed with water (20 mL), brine (15 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The crude was purified by column chromatography to get 3-methyl-4-

20 (oxazol-5-yl)aniline (610 mg, 65%).

Preparation of 5-(3-methyl-4-nitrophenyl)oxazole

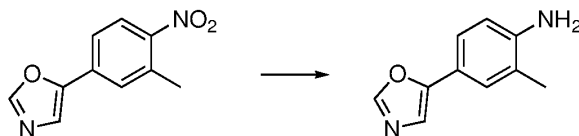


To a stirred solution of 3-methyl-4-nitrobenzaldehyde (2.01 g, 12.1 mmol) and 1-(isocyanomethane)sulfonyl-4-

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methylbenzene (2.6 g, 13.3 mmol) in MeOH (50 mL) was added K_2CO_3 (3.34 g, 24.2 mmol) and the reaction mixture was heated to reflux for 2 h. After complete consumption of starting material by TLC, the reaction was cooled to
5 room temperature, solvent was evaporated under reduced pressure, the residue was treated with saturated aqueous solution of $NaHCO_3$ (40 mL), and extracted with ethyl acetate (3 x 40 mL). The organic layers were combined, washed with water (30 mL) and brine (20 mL), dried over
10 Na_2SO_4 , and concentrated under reduced pressure. The crude was purified by column chromatography using silica (to get 5-(3-methyl-4-nitrophenyl)oxazole (1.9 g, 76%).

Preparation of 2-methyl-4-(oxazol-5-yl)aniline

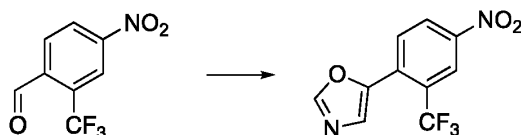


15 To a stirred solution of 5-(3-methyl-4-nitrophenyl)oxazole (1.8 g, 5.39 mmol) in methanol (20 mL) was added Raney-Nickel (2.0 g) at room temperature. The reaction mixture was stirred under H_2 atmosphere for 18 h. After complete consumption of starting material, reaction mixture was
20 filtered through a bed of celite and the filtrate was concentrated under reduced pressure. The crude was purified by column chromatography to get 2-methyl-4-(oxazol-5-yl)aniline (1.3 g, 84%).

LCMS:174.7 (M+H)

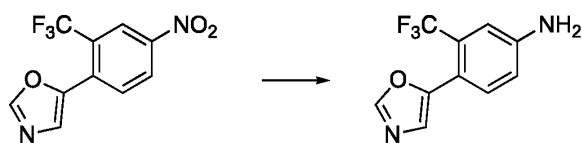
25 Preparation of 5-(4-nitro-2-(trifluoromethyl)phenyl)oxazole

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To a stirred solution of 4-nitro-2-(trifluoromethyl)benzaldehyde (2.0 g, 9.13 mmol) and 1-(isocyanomethane)sulfonyl-4-methylbenzene (2.05 g, 10.5
 5 mmol) in MeOH (50 mL) was added K_2CO_3 (2.52 g, 18.26 mmol) and the reaction mixture was heated to reflux for 2 h. After consumption of starting material by TLC, the reaction mixture was cooled to room temperature, the solvent was evaporated under reduced pressure, the residue
 10 was treated with saturated aqueous solution of $NaHCO_3$ (20 mL), and extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with water (30 mL), brine (20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure to get crude which was purified by column
 15 chromatography to get 5-(4-nitro-2-(trifluoromethyl)phenyl)oxazole (1.66 g, 72%).

Preparation of 4-(oxazol-5-yl)-3-(trifluoromethyl)aniline

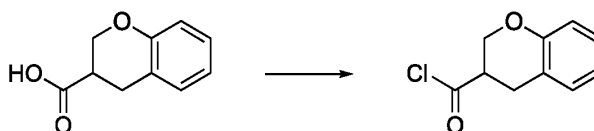


To a stirred solution of 5-(4-nitro-2-(trifluoromethyl)phenyl)oxazole (1.545 g, 5.99 mmol) in
 20 ethanol (30 mL) was added tin(II) chloride dihydrate (5.40 g, 23.95 mmol) at room temperature. The mixture was cooled to 0°C and conc. HCl (3.5 mL) was added drop wise. The reaction mixture was then stirred for 2.0 h at 80°C. After
 25 completion of the reaction by TLC, the reaction mixture

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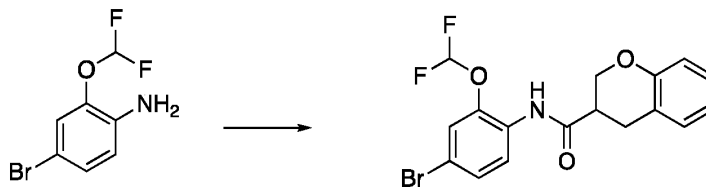
was cooled to room temperature, diluted with saturated aqueous solution of NaHCO_3 (70 mL), and extracted with ethyl acetate (3 x 50 mL). Organic layers were combined, washed with water (40 mL), brine (30 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The crude was purified by column chromatography to get 4-(oxazol-5-yl)-3-(trifluoromethyl)aniline (1.13 mg, 83%).

Preparation of Chroman-3-carbonyl chloride



To a solution of chroman-3-carboxylic acid (750 mg, 4.21 mmol) in dry dichloromethane (10 mL) was added thionyl chloride (0.45 mL, 6.32 mmol) at 0° C followed by DMF (catalytic). After the addition, the reaction mixture was warmed to room temperature and heated to reflux for 2.0 h. The reaction mass was cooled to room temperature, the solvent was evaporated under reduced pressure, and dried under vacuum.

Preparation of N-(4-bromo-2-(difluoromethoxy)phenyl)chroman-3-carboxamide

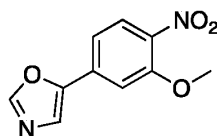


A solution of chroman-3-carbonyl chloride in dry dichloromethane (10 mL) was added to the mixture of 4-bromo-2-(difluoromethoxy)aniline (600 mg, 2.521 mmol) and

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triethylamine (1.1 mL, 7.563 mmol) in dry dichloromethane (10 mL) at 0° C. After the addition, reaction was slowly warmed to room temperature over 3 h. The reaction was diluted with dichloromethane (5 mL), washed with water (10 mL) and brine (15 mL), dried over Na₂SO₄, and concentrated under reduced pressure to get crude. Purification of the crude by column chromatography gave N-(4-bromo-2-(difluoromethoxy)phenyl)chroman-3-carboxamide (520 mg, 62%).

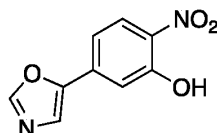
10 Preparation of 5-(3-methoxy-4-nitrophenyl)oxazole



To a stirred solution of 3-methoxy-4-nitrobenzaldehyde (2.5 g, 13.80 mmol) and toluenesulfonylmethyl isocyanide (3.1 g, 15.87 mmol) in MeOH (60 mL) was added K₂CO₃ (3.8 g, 27.60 mmol) and the reaction mixture was heated to reflux for 2 h. After consumption of starting material by TLC, the reaction mixture was cooled to room temperature, the solvent was evaporated under reduced pressure, the residue was treated with saturated aqueous solution of NaHCO₃ (40 mL), and extracted with ethyl acetate (3 x 40 mL). The organic layer was washed with water (40 mL), brine (30 mL), dried over Na₂SO₄, and concentrated under reduced pressure to get the crude product which was triturated with dichloromethane /hexane to get 5-(3-methoxy-4-nitrophenyl)oxazole (2.4 g, 78%).

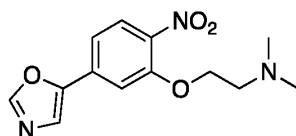
Preparation of 2-nitro-5-(oxazol-5-yl)phenol

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To a stirred solution of 5-(3-methoxy-4-nitrophenyl)oxazole (2.0 g, 9.09 mmol) in dry dichloromethane (50 mL) was added BBr₃ (1M in dichloromethane, 22.7 mL, 22.72 mmol) at 0° C under N₂. The resulting mixture was allowed to warm to room temperature and stirred for 2h. After consumption of starting material by TLC, the reaction mixture was quenched with ice water (30 mL) and stirred for 30 min at room temperature. The reaction mixture was filtered and the solids were washed with dichloromethane (2 x 25 mL). The filtrate was washed with water (30 mL), brine (20 mL) dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by column chromatography using silica gel to get 2-nitro-5-(oxazol-5-yl)phenol (1.7 g, 90%) as solid.

Preparation of N-dimethyl-2-(2-nitro-5-(oxazol-5-yl)phenoxy)ethanamine

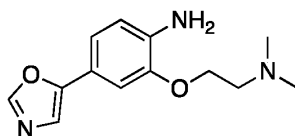


A mixture of 2-nitro-5-(oxazol-5-yl)phenol (1.65 g, 8.01 mmol), dimethylaminoethyl chloride hydrochloride (1.9 g, 13.2 mmol), K₂CO₃ (6.6 g, 47.7 mmol), potassium iodine (215 mg, 1.29 mmol), and DMF (35 mL) was heated at 100 °C for 2 h. The reaction was monitored by TLC (part of the starting materials remained unreacted), the reaction mixture was

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cooled to room temperature, and concentrated. The residue was diluted with saturated aqueous solution of NH_4Cl (20 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was washed with water (50 mL), brine (40 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The crude was purified by column chromatography to get *N,N*-dimethyl-2-(2-nitro-5-(oxazol-5-yl)phenoxy)ethanamine (750 mg) as solid.

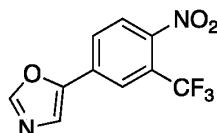
Preparation of 2-(2-(dimethylamino)ethoxy)-4-(oxazol-5-yl)aniline



To a stirred solution of *N,N*-dimethyl-2-(2-nitro-5-(oxazol-5-yl)phenoxy)ethanamine (725 mg, 2.62 mmol) in ethanol (20 mL) was added tin(II) chloride dihydrate (2.95 g, 13.08 mmol) and the reaction mixture was heated to 65-70 °C for 1.5 h. After consumption of starting material by TLC, the reaction mixture was cooled room temperature, basified with saturated aqueous solution of Na_2CO_3 (45 mL), diluted with dichloromethane (60 mL), and aqueous phase was extracted with dichloromethane (3 x 30 mL). The organic layers were combined, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude was purified by column chromatography to get 2-(2-(dimethylamino)ethoxy)-4-(oxazol-5-yl)aniline (575 mg, 86%).

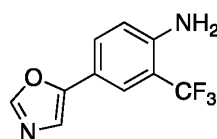
Preparation of 5-(4-nitro-2-(trifluoromethyl)phenyl)oxazole

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To a stirred solution of 4-nitro-2-(trifluoromethyl)benzaldehyde (2.0 g, 9.13 mmol) and toluenesulfonylmethyl isocyanide (2.05 g, 10.5 mmol) in
5 MeOH (50 mL) was added K₂CO₃ (2.52 g, 18.26 mmol) and the reaction mixture was heated to reflux for 2 h. After consumption of starting material by TLC, the reaction mixture was cooled to room temperature, the solvent was evaporated under reduced pressure, the residue was treated
10 with saturated aqueous solution of NaHCO₃ (20 mL), and extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with water (30 mL), brine (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure to get the crude product which was purified by column
15 chromatography to get 5-(4-nitro-2-(trifluoromethyl)phenyl)oxazole (1.66 g, 72%) as solid.

Preparation of 4-(oxazol-5-yl)-3-(trifluoromethyl)aniline

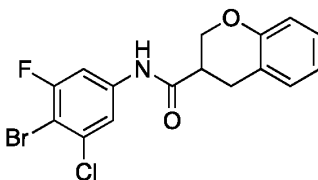


To a stirred solution of 5-(4-nitro-2-(trifluoromethyl)phenyl)oxazole (1.545 g, 5.99 mmol) in
20 ethanol (30 mL) was added tin(II) chloride dihydrate (5.40 g, 23.95 mmol) at room temperature. The mixture was cooled to 0°C and conc. HCl (3.5 mL) was added drop wise. The reaction mixture was then stirred for 2.0 h at 80°C. After
25 completion of the reaction by TLC, the reaction mixture

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was cooled to room temperature, diluted with saturated aqueous solution of NaHCO₃ solution (70 mL), and extracted with ethyl acetate (3 x 50 mL). Organic layers were combined, washed with water (40 mL), brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude was purified by column chromatography to get 4-(oxazol-5-yl)-3-(trifluoromethyl)aniline (1.13 g, 83%).

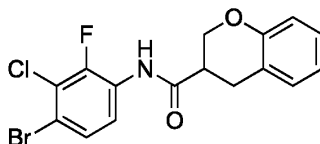
Preparation of *N*-(4-bromo-3-chloro-5-fluorophenyl)chroman-3-carboxamide



A solution of chroman-3-carbonyl chloride in dry dichloromethane (10 mL) was added to the mixture of 4-bromo-3-chloro-5-fluoroaniline (300 mg, 1.34 mmol) and triethylamine (0.56 mL, 4.00 mmol) in dry dichloromethane (10 mL) at 0° C. After the addition, reaction was slowly warmed to room temperature over 3 h. The reaction was diluted with dichloromethane (10 mL), washed with water (10 mL) and brine (15 mL), dried over Na₂SO₄, and concentrated under reduced pressure to get crude. Purification of the crude by column chromatography gave *N*-(4-bromo-3-chloro-5-fluorophenyl)chroman-3-carboxamide (280 mg, 49%) as solid.

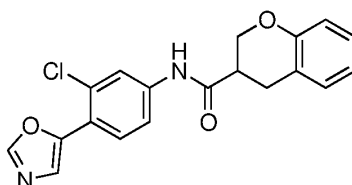
Preparation of *N*-(4-bromo-3-chloro-2-fluorophenyl)chroman-3-carboxamide

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A solution of chroman-3-carbonyl chloride in dry dichloromethane (10 mL) was added to the mixture of 4-bromo-3-chloro-2-fluoroaniline (600 mg, 2.673 mmol) and triethylamine (1.1 mL, 8.02 mmol) in dry dichloromethane (10 mL) at 0° C. After the addition, reaction was slowly warmed to room temperature over 3 h. The reaction mixture was monitored by TLC. After maximum conversion, the reaction mixture was diluted with dichloromethane (5 mL), washed with water (10 mL) and brine (15 mL), dried over sodium sulphate, and concentrated under reduced pressure to get crude *N*-(4-bromo-3-chloro-2-fluorophenyl)chroman-3-carboxamide. Purification of the crude by column chromatography gave *N*-(4-bromo-3-chloro-2-fluorophenyl)chroman-3-carboxamide (320 mg, 31.2%) as solid.

Compound (1): first (-)-*N*-(3-chloro-4-(1,3-oxazol-5-yl)phenyl)chromane-3-carboxamide



To a stirred solution of 3-chloro-4-(oxazol-5-yl)aniline (100 mg, 0.51 mmol) and chromane-3-carboxylic acid (109 mg, 0.61 mmol) in DMF (1 mL) were added DIPEA (0.26 mL) and HATU (392 mg, 1.03 mmol) at room temperature

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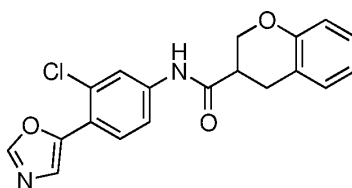
and the reaction was stirred for 16 h at room temperature. After completion of the reaction, the reaction mixture was purified by preparative HPLC to yield *N*-(3-chloro-4-(1,3-oxazol-5-yl)phenyl)chromane-3-carboxamide (34 mg, 18%).

5 The racemic product was separated by chiral chromatography using Chiral Separation Method C to yield Compound (1), which is characterized by retention time = 4.76 min (first eluted from the column).

Analytical HPLC Method A. Rt: 1.73 min; MS: 355 (M+H).

10 $[\alpha]_D^{25} = -7.57$ (589 nm, c=0.49, DMSO).

Compound (2): second (+)-*N*-(3-chloro-4-(1,3-oxazol-5-yl)phenyl)chromane-3-carboxamide



To a stirred solution of 3-chloro-4-(oxazol-5-yl)aniline (100 mg, 0.51 mmol) and chromane-3-carboxylic acid (109 mg, 0.61 mmol) in DMF (1 mL) were added DIPEA (0.26 mL) and HATU (392 mg, 1.03 mmol) at room temperature and the reaction was stirred for 16 h at room temperature. After completion of the reaction, the reaction mixture was purified by preparative HPLC to yield *N*-(3-chloro-4-(1,3-oxazol-5-yl)phenyl)chromane-3-carboxamide (34 mg, 18%). The racemic product was separated by chiral chromatography using Chiral Separation Method C to yield Compound (2), which is characterized by retention time = 6.04 min (second eluted from the column).

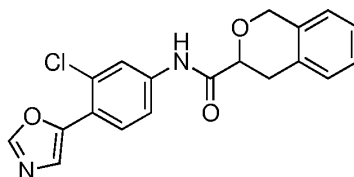
15
20
25

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Analytical HPLC Method A. Rt: 1.73 min; MS: 355 (M+H).

$[\alpha]_D^{25} = +5.83$ (589 nm, c=0.55, DMSO).

Compound (3): *N*-(3-chloro-4-(oxazol-5-yl)phenyl)isochromane-3-carboxamide



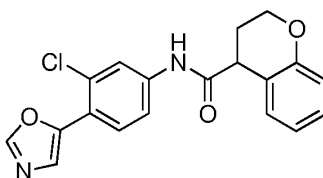
5

The title compound was prepared from isochromane-3-carboxylic acid and 3-chloro-4-(oxazol-5-yl)aniline using coupling procedure A and preparative HPLC Method A (yield 33%).

10 MS: 355.0 (M+H).

^1H NMR (400 MHz, DMSO- d_6) δ 10.25 (s, 1H), 8.53 (s, 1H), 8.11 (d, $J = 1.7$ Hz, 1H), 7.84 (dd, $J = 8.7, 1.9$ Hz, 1H), 7.79 (d, $J = 8.7$ Hz, 1H), 7.72 (s, 1H), 7.25 - 7.18 (m, 3H), 7.16 - 7.09 (m, 1H), 5.04 - 4.85 (m, 2H), 4.48 - 4.37
15 (m, 1H), 3.19 - 2.95 (m, 2H).

Compound (4): *N*-(3-chloro-4-(oxazol-5-yl)phenyl)chromane-4-carboxamide



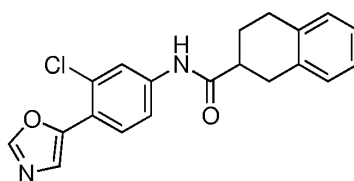
The title compound was prepared from 3,4-dihydro-2H-1-benzopyran-4-carboxylic acid and 3-chloro-4-(oxazol-5-yl)aniline using
20 coupling procedure A and preparative HPLC Method A (yield 33%).

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yl)aniline using coupling procedure A and preparative HPLC Method A (yield 12%).

MS: 355.0 (M+H).

Compound (5): *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-1,2,3,4-tetrahydronaphthalene-2-carboxamide



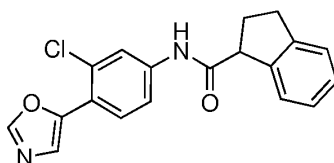
A mixture of 3-chloro-4-(oxazol-5-yl)aniline (110 mg, 0,567 mmol), 2,3-dihydro-1*H*-indene-1-carboxylic acid (105 mg, 0,595 mmol) and *N*-hydroxybenzotriazole (85 mg, 0,624 mmol) was dissolved in 1 ml of dry dimethyl acetamide and cooled to -10°C. Then 106 mg (0.68 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide were added and the mixture was stirred for 16 h at room temperature. 30 ml of water were added, the obtained precipitate was filtered, washed three times with 10 ml of water, once with 3 ml of isopropanol and twice with 10 ml of hexane. Then it was dried on air at 50°C. 110 mg were obtained (yield 55%).

MS: 353.0 (M+H).

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.37 (s, 1H), 8.52 (s, 1H), 8.04 (d, *J* = 2.0 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.70 (s, 1H), 7.65 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.18 - 7.00 (m, 4H), 2.94 (d, *J* = 7.8 Hz, 2H), 2.89 - 2.72 (m, 3H), 2.18 - 2.01 (m, 1H), 1.87 - 1.69 (m, 1H).

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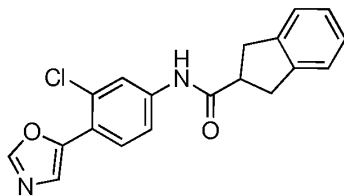
Compound (6): *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-2,3-dihydro-1*H*-indene-1-carboxamide



The title compound was prepared from 2,3-dihydro-1*H*-indene-1-carboxylic acid and 3-chloro-4-(oxazol-5-yl)aniline using coupling procedure A and preparative HPLC Method A (yield 9%).

MS: 339.0 (M+H).

Compound (7): *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-2,3-dihydro-1*H*-indene-2-carboxamide

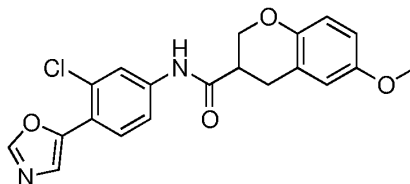


The title compound was prepared from 2,3-dihydro-1*H*-indene-2-carboxylic acid and 3-chloro-4-(oxazol-5-yl)aniline using coupling procedure A and preparative HPLC Method A (yield 14%).

MS: 339.2 (M+H).

Compound (8): *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-6-methoxychromane-3-carboxamide

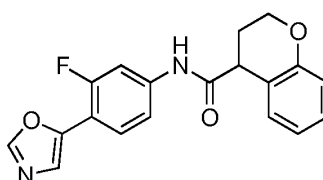
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To a stirred solution of 3-chloro-4-(oxazol-5-yl)aniline (200 mg, 1.03 mmol) and 6-methoxy-3,4-dihydro-2H-1-benzopyran-3-carboxylic acid (278.76 mg, 1.34 mmol) in DMF
5 (2 mL) were added DIPEA (0.52 mL) and HATU (784mg, 2.06 mmol) at room temperature and the reaction was stirred for 16 h at room temperature. After completion of the reaction, the reaction mixture was purified by preparative HPLC to yield N-(3-chloro-4-(oxazol-5-yl)phenyl)-6-methoxychromane-3-carboxamide (143 mg, 36%).
10

Analytical HPLC Method A. Rt: 1.73 min; MS: 385.2 (M+H).

Compound (9): N-(3-fluoro-4-(oxazol-5-yl)phenyl)chromane-4-carboxamide



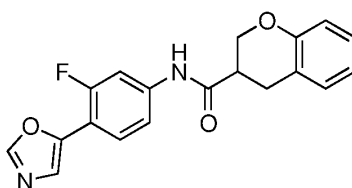
15 To a stirred solution of 3-fluoro-4-(1,3-oxazol-5-yl)aniline (150 mg, 0.84 mmol) and 3,4-dihydro-2H-1-benzopyran-4-carboxylic acid (195.21 mg, 1.09 mmol) in DMF (2 mL) were added DIPEA (0.44 mL) and HATU (640 mg, 1.68 mmol) at room temperature and the reaction was
20 stirred for 16 h at room temperature. After completion of the reaction, the reaction mixture was purified by

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preparative HPLC to yield *N*-(3-fluoro-4-(oxazol-5-yl)phenyl)chromane-4-carboxamide (102 mg, 35%).

Analytical HPLC Method A. Rt: 1.50 min; MS: 339.2 (M+H).

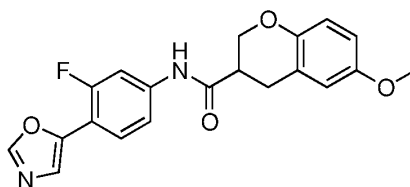
Compound (10): *N*-(3-fluoro-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide



To a stirred solution of 3-fluoro-4-(1,3-oxazol-5-yl)aniline (100 mg, 0.56 mmol) and 3,4-dihydro-2H-1-benzopyran-3-carboxylic acid (130.7 mg, 0.73 mmol) in DMF
10 (1 mL) were added DIPEA (0.29 mL) and HATU (427 mg, 1.12 mmol) at room temperature and the reaction was stirred for 16 h at room temperature. After completion of the reaction, the reaction mixture was purified by preparative HPLC to yield *N*-(3-fluoro-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide (70 mg, 36%).
15

Analytical HPLC Method A. Rt: 1.62 min; MS: 339.2 (M+H).

Compound (11): *N*-(3-fluoro-4-(oxazol-5-yl)phenyl)-6-methoxychromane-3-carboxamide

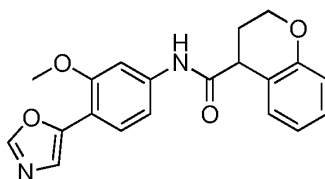


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To a stirred solution of 3-fluoro-4-(1,3-oxazol-5-yl)aniline (150 mg, 0.84 mmol) and 6-methoxy-3,4-dihydro-2H-1-benzopyran-3-carboxylic acid (227.86 mg, 1.09 mmol) in DMF (1.5 mL) were added DIPEA (0.44 mL) and HATU (640.5 mg, 1.68 mmol) at room temperature and the reaction was stirred for 16 h at room temperature. After completion of the reaction, the reaction mixture was purified by preparative HPLC to yield *N*-(3-fluoro-4-(oxazol-5-yl)phenyl)-6-methoxychromane-3-carboxamide (121 mg, 38%).

10 Analytical HPLC Method A. Rt: 1.64 min; MS: 369.3 (M+H).

Compound (12): *N*-(3-methoxy-4-(oxazol-5-yl)phenyl)chromane-4-carboxamide

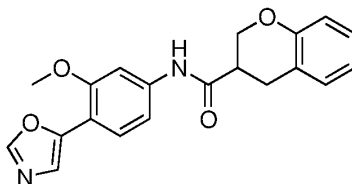


To a stirred solution of 3-methoxy-4-(oxazol-5-yl)aniline (75 mg, 0.395 mmol) and 3,4-dihydro-2H-1-benzopyran-4-carboxylic acid (105.3 mg, 0.592 mmol) in DMF (3 mL) were added DIPEA (0.15 mL) and HATU (226 mg, 0.592 mmol) at room temperature and the reaction was stirred for 12 h at room temperature. After completion of the reaction, the reaction mixture was purified by preparative HPLC to yield *N*-(3-methoxy-4-(oxazol-5-yl)phenyl)chromane-4-carboxamide (60.07 mg, 44%).

Analytical HPLC Method A. Rt: 1.42 min; MS: 351.2 (M+H).

Compound (13): *N*-(3-methoxy-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide

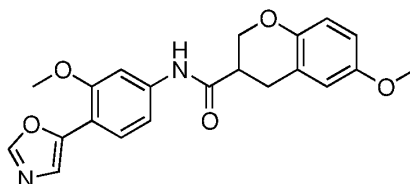
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To a stirred solution of 3-methoxy-4-(oxazol-5-yl)aniline (75 mg, 0.395 mmol) and 3, 4-dihydro-2H-1-benzopyran-3-carboxylic acid (105.3 mg, 0.592 mmol) in DMF (3 mL) were
5 added DIPEA (0.15 mL) and HATU (226 mg, 0.592 mmol) at room temperature and the reaction was stirred for 12 h at room temperature. After completion of the reaction, the reaction mixture was purified by preparative HPLC to yield *N*-(3-methoxy-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide
10 (77.6 mg, 56%).

Analytical HPLC Method A. Rt: 1.59 min; MS: 351.2 (M+H).

Compound (14): 6-methoxy-*N*-(3-methoxy-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide



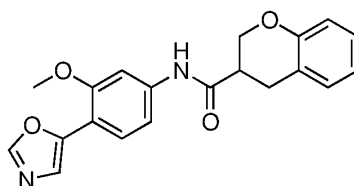
15 To a stirred solution of 3-methoxy-4-(oxazol-5-yl)aniline (75 mg, 0.395 mmol) and 6-methoxy-3,4-dihydro-2H-1-benzopyran-3-carboxylic acid (123.1 mg, 0.592 mmol) in DMF (3 mL) were added DIPEA (0.15 mL) and HATU (226 mg, 0.592 mmol) at room temperature and the reaction was
20 stirred for 12 h at room temperature. After completion of the reaction, the reaction mixture was purified by

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preparative HPLC to yield 6-methoxy-*N*-(3-methoxy-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide (72.3 mg, 48%).

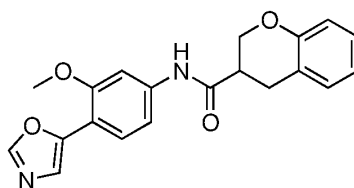
Analytical HPLC Method A. Rt: 1.55 min; MS: 381.2 (M+H).

Compound (15): first *N*-(3-methoxy-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide



The racemic *N*-(3-methoxy-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide (compound (13)) was subjected to chiral separation using Chiral Separation Method K. First *N*-(3-methoxy-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide was identified using Chiral Separation Method G, Rt: 9.09 min. MS: 351.25 (M+H).

Compound (16): second *N*-(3-methoxy-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide



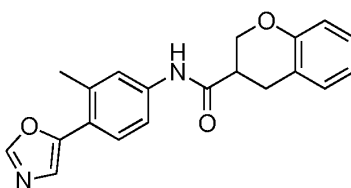
The racemic *N*-(3-methoxy-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide (compound (13)) was subjected to chiral separation using Chiral Separation Method K. First *N*-(3-methoxy-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide was

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identified using Chiral Separation Method G, Rt: 10.85 min.

MS: 351.25 (M+H).

Compound (17): *N*-(3-methyl-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide

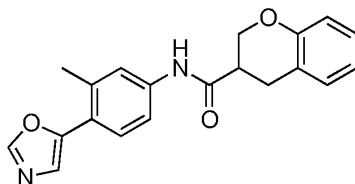


A solution of chroman-3-carbonyl chloride prepared freshly in dry dichloromethane (10 mL) was added to the mixture of 3-methyl-4-(oxazol-5-yl)aniline (500 mg, 2.87 mmol) and triethylamine (1.25 mL, 8.61mmol) in dry dichloromethane (10 mL) at 0°C. After the addition, reaction was slowly warmed to room temperature over 3 h. The reaction was monitored by TLC, after maximum conversion (part of the starting materials remained unreacted) diluted with dichloromethane (5 mL), washed with water (10 mL) and brine (15 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude was purified by column chromatography followed by trituration with MTBE to obtain *N*-(3-methyl-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide (240 mg, 25%).

Analytical HPLC Method B. Rt: 2.47 min, LCMS: 335.08 (M+H).

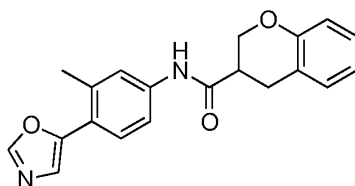
Compound (18): first *N*-(3-methyl-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide

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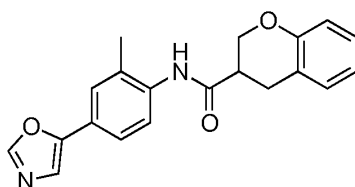
Chiral separation of racemic *N*-(3-methyl-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide (Compound (17)) using Chiral Separation Method A yields the title compound (65.6
 5 mg) characterized by retention time = 5.41. (First compound eluted from the column)

Compound (19) : second *N*-(3-methyl-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide



10 Chiral separation of racemic *N*-(3-methyl-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide (Compound (17)) using Chiral Separation Method A yields the title compound (75.6 mg) characterized by retention time = 11.73 min. Second compound eluted from the column)

15 **Compound (20) :** *N*-(2-methyl-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide



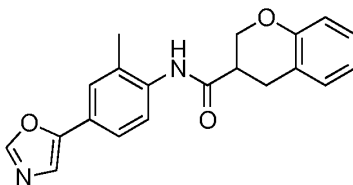
A solution of chroman-3-carbonyl chloride prepared freshly

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in dry dichloromethane (10 mL) was added to the mixture of 3-methyl-4-(oxazol-5-yl)aniline (500 mg, 2.87 mmol) and triethylamine (1.25 mL, 8.61mmol) in dry dichloromethane (10 mL) at 0° C. After the addition, reaction was slowly
5 warmed to room temperature over 3h. The reaction was monitored by TLC, after maximum conversion (part of the starting materials remained unreacted) diluted with dichloromethane (5 mL), washed with water (10 mL) and brine (15 mL), dried over Na₂SO₄, and concentrated under
10 reduced pressure. The crude was purified by column chromatography followed by trituration with MTBE to give *N*-(2-methyl-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide (210 mg, 22%).

Analytical HPLC Method B. Rt: 2.56 min, LCMS:335.1

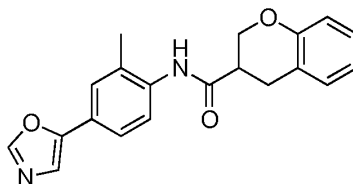
15 **Compound (21):** first *N*-(2-methyl-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide



Chiral separation of Compound (20) using Chiral Separation Method A yields (69.9 mg) characterized by retention time
20 = 5.41 min. (First eluted compound)

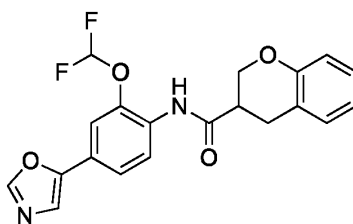
Compound (22): second *N*-(2-methyl-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide

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Chiral separation of Compound (20) using Chiral Separation Method A yields (73.2 mg) characterized by retention time = 11.73 min. (Second eluted compound)

- 5 **Compound (23) :** *N*-(2-(difluoromethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide



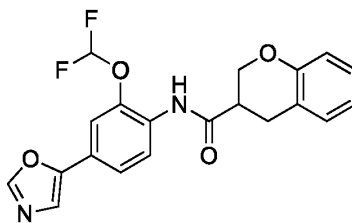
To a stirred solution of *N*-(4-bromo-2-(difluoromethoxy)phenyl)chroman-3-carboxamide (400 mg, 1.01 mmol) in 1,4-dioxane/water (20 mL, 2:1) 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (255 mg, 1.31 mmol) and Na₂CO₃ (213 mg, 2.02 mmol) were added under argon. The reaction mixture was degassed with argon for 20 min. Then Pd(PPh₃)₄ (58 mg, 0.05 mmol) was added and the mixture degassed with argon for 5 min. The reaction mixture was sealed and stirred at 80⁰ C for 10 h. After the maximum consumption of the starting material, the reaction mixture was cooled to room temperature, diluted with water (5.0 mL), and extracted with EtOAc (2 x 50 mL). Organic layers were combined, washed with water (10 mL) and brine (10 mL), dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The crude was purified

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column chromatography to give racemic *N*-(2-(difluoromethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide (152 mg, 39%).

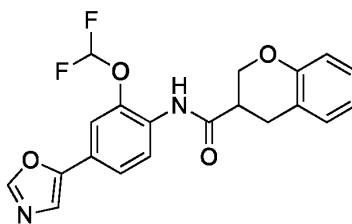
Analytical HPLC Method B. Rt: 2.50 min, LCMS: 387 (M+H).

- 5 **Compound (24):** first *N*-(2-(difluoromethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide



- Chiral separation of racemic *N*-(2-(difluoromethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide Compound (23)
10 using Chiral Separation Method C yields Compound (24)
(44.9 mg) characterized by retention time = 6.64 min.
(First eluted compound)

Compound (25): second *N*-(2-(difluoromethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide



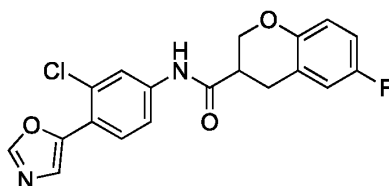
15

Chiral separation of racemic *N*-(2-(difluoromethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide Compound (23)
using Chiral Separation Method C yields Compound (25)

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(47.0 mg) characterized by retention time = 8.67 min.
(Second eluted compound)

Compound (26): first *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-6-fluorochromane-3-carboxamide



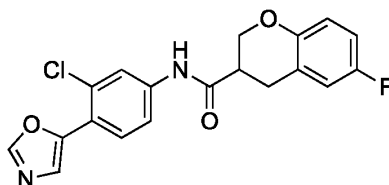
5

The racemic compound was prepared from 6-fluorochromane-3-carboxylic acid and 3-chloro-4-(oxazol-5-yl)aniline using coupling procedure A and preparative HPLC Method A.

MS: 373.0 (M+H).

10 Chiral separation of racemic *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-6-fluorochromane-3-carboxamide compound was accomplished using Chiral Separation Method H to yield Compound (26) characterized by retention time = 10.9 min.
(First eluted compound)

15 **Compound (27):** second *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-6-fluorochromane-3-carboxamide

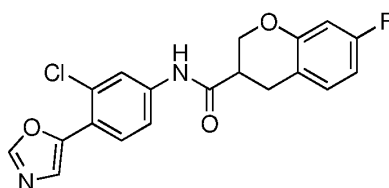


Chiral separation of racemic *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-6-fluorochromane-3-carboxamide compound was
20 accomplished using Chiral Separation Method H to yield

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compound 26 characterized by retention time = 18.9 min.
(Second eluted compound)

Compound (28): racemic *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-7-fluorochromane-3-carboxamide

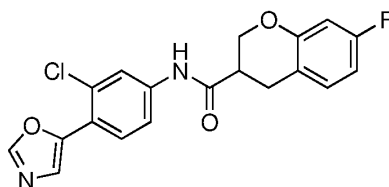


5

The racemic compound was prepared from 7-fluorochromane-3-carboxylic acid (1.1 mmol) and 3-chloro-4-(oxazol-5-yl)aniline using coupling procedure A. The racemic product was purified by preparative HPLC method A (511 mg, 71%
10 yield).

MS: 373.0 (M+H).

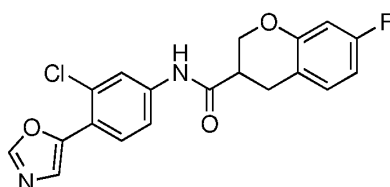
Compound (29): first *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-7-fluorochromane-3-carboxamide



15 Chiral separation of racemic *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-7-fluorochromane-3-carboxamide compound was accomplished using Chiral Separation Method I to yield compound 26 (100.3 mg) characterized by retention time = 11.5 min. (First eluted compound)

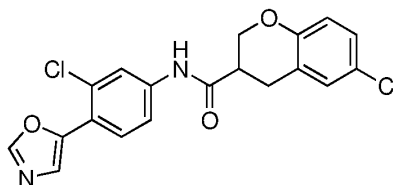
- 120 -

Compound (30): second *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-7-fluorochromane-3-carboxamide



Chiral separation of racemic *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-7-fluorochromane-3-carboxamide compound was accomplished using Chiral Separation Method I to yield compound 26 (87.1 mg) characterized by retention time = 15.8 min. (Second eluted compound)

Compound (31): 6-chloro-*N*-(3-chloro-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide

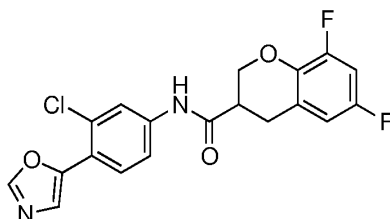


The title compound was prepared from 6-chlorochromane-3-carboxylic acid and 3-chloro-4-(oxazol-5-yl)aniline using coupling procedure A and preparative HPLC Method A (yield 16%).

MS: 389.0 (M+H).

Compound (32): *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-6,8-difluorochromane-3-carboxamide

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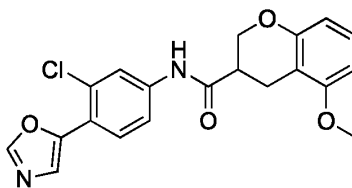


The title compound was prepared from 6,8-difluorochromane-3-carboxylic acid and 3-chloro-4-(oxazol-5-yl)aniline using coupling procedure A and preparative HPLC Method A
 5 (yield 18%).

MS: 391.0 (M+H).

¹H NMR (500 MHz, DMSO-*d*₆) δ 10.58 (s, 1H), 8.52 (s, 1H), 8.01 – 7.97 (m, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.71 (s, 1H), 7.61 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.14 – 7.06 (m, 1H),
 10 6.93 (d, *J* = 8.4 Hz, 1H), 4.54 – 4.48 (m, 1H), 4.16 – 4.08 (m, 1H), 3.13 – 3.08 (m, 1H), 3.08 – 3.00 (m, 2H).

Compound (33): *N*-(3-chloro-4-(oxazol-5-yl)phenyl)-5-methoxychromane-3-carboxamide

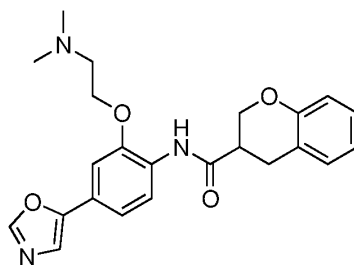


15 The title compound was prepared from 5-methoxychromane-3-carboxylic acid and 3-chloro-4-(oxazol-5-yl)aniline using coupling procedure A and preparative HPLC Method A. (Yield: 16.6%)

MS: 385.0 (M+H)

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Compound (34): *N*-(2-(2-(dimethylamino)ethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide

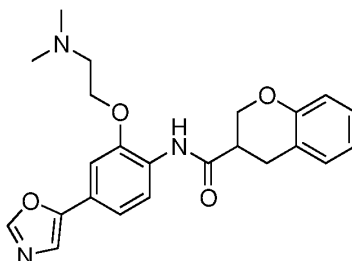


A solution of chroman-3-carbonyl chloride in dry
5 dichloromethane (10 mL) was added to the mixture of 2-(2-(
(dimethylamino)ethoxy)-4-(oxazol-5-yl)aniline (535 mg,
2.16 mmol) and triethylamine (0.9 mL, 6.50 mmol) in dry
dichloromethane (10 mL) at 0° C. After the addition,
reaction was slowly warmed to room temperature over 3 h.
10 The reaction was monitored by TLC. After maximum
conversion (part of the starting materials remained
unreacted) the reaction mixture was diluted with
dichloromethane (10 mL), washed with water (30 mL) and
brine (20 mL), dried over Na₂SO₄, and concentrated under
15 reduced pressure. The crude mixture was purified by column
chromatography to give racemic *N*-(2-(2-(
(dimethylamino)ethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-
carboxamide (410 mg, 45%) as a solid.

Analytical HPLC Method C. Rt: 2.03 min; MS: 408.2 (M+H).

20 **Compound (35):** first *N*-(2-(2-(dimethylamino)ethoxy)-4-(
(oxazol-5-yl)phenyl)chroman-3-carboxamide

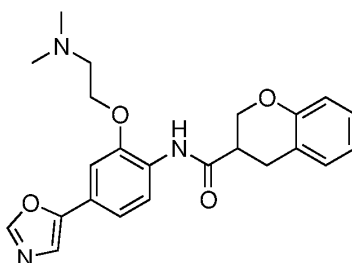
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The racemic *N*-(2-(2-(dimethylamino)ethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide (Compound (34)) was subjected to chiral separation using Chiral Separation
5 Method D. First *N*-(2-(2-(dimethylamino)ethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide was eluted first at 4.16 min (83.8 mg).

Analytical HPLC Method C. Rt: 2.03 min; MS: 408.2 (M+H).

Compound (36): second *N*-(2-(2-(dimethylamino)ethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide
10

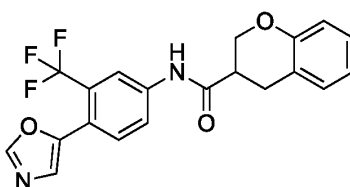


The racemic *N*-(2-(2-(dimethylamino)ethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide (Compound (34)) was subjected to chiral separation using Chiral Separation
15 Method D. Second *N*-(2-(2-(dimethylamino)ethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide was eluted first at 7.89 min (56.3 mg).

Analytical HPLC Method C. Rt: 2.03 min; MS: 408.2 (M+H).

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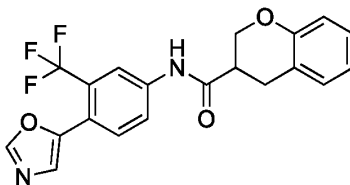
Compound (37) : racemic N-(4-(oxazol-5-yl)-3-(trifluoromethyl)phenyl)chromane-3-carboxamide



A solution of chroman-3-carbonyl chloride (in dry
5 dichloromethane (10 mL) was added to the mixture of 4-(oxazol-5-yl)-3-(trifluoromethyl)aniline (600 mg, 2.63 mmol) and triethylamine (1.1 mL, 7.90 mmol) in dry dichloromethane (10 mL) at 0° C. After the addition, reaction was slowly warmed to room temperature over 3 h.
10 The reaction was monitored by TLC, after maximum conversion (part of the starting materials remained unreacted) diluted with dichloromethane (5 mL), washed with water (20 mL) and brine (15 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude was
15 purified by column chromatography using silica gel to give racemic N-(4-(oxazol-5-yl)-3-(trifluoromethyl)phenyl)chroman-3-carboxamide (350 mg, 35%) as solid.

Analytical HPLC Method C. Rt: 2.79 min; MS: 389.1 (M+H).

20 **Compound (38) :** first N-(4-(oxazol-5-yl)-3-(trifluoromethyl)phenyl)chromane-3-carboxamide

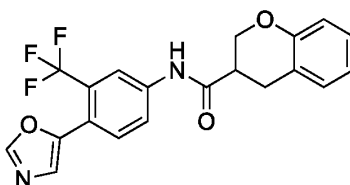


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The racemic *N*-(4-(oxazol-5-yl)-3-(trifluoromethyl)phenyl)chroman-3-carboxamide was subjected to chiral separation using Chiral Separation Method E. First *N*-(2-(2-(dimethylamino)ethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide was eluted at 2.69 min (70.2 mg).

Analytical HPLC Method C. Rt: 2.79 min; MS: 389.1 (M+H).

Compound (39): second *N*-(4-(oxazol-5-yl)-3-(trifluoromethyl)phenyl)chromane-3-carboxamide

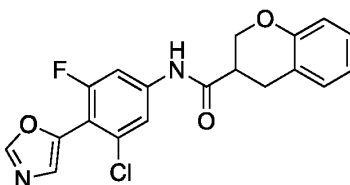


10

The racemic *N*-(4-(oxazol-5-yl)-3-(trifluoromethyl)phenyl)chroman-3-carboxamide was subjected to chiral separation using Chiral Separation Method E. Second *N*-(2-(2-(dimethylamino)ethoxy)-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide was eluted at 3.24 min (71.6 mg).

Analytical HPLC Method C. Rt: 2.79 min; MS: 389.1 (M+H).

Compound (40): second *N*-(3-chloro-5-fluoro-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide



20

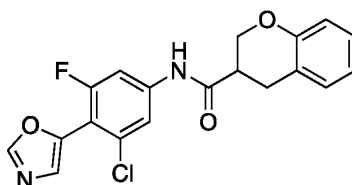
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To a stirred solution of *N*-(4-bromo-3-chloro-2-fluorophenyl)chroman-3-carboxamide (100 mg, 0.260 mmol) in 1,4-dioxane/water (6 mL, 2:1) 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (66 mg, 0.338 mmol), and
5 Na_2CO_3 (55 mg, 0.521 mmol) were added under argon. The reaction mixture was degassed with argon for 20 min. Then $\text{Pd}(\text{dppf})\text{Cl}_2$ - dichloromethane complex (10.6 mg, 0.013 mmol) was added and degassed with argon for 5 min. The reaction mixture was sealed and stirred at 80°C for 8.0 h. The
10 reaction mixture was cooled to room temperature, diluted with water (5.0 mL), and extracted with EtOAc (2 x 30 mL). Organic layers were combined, washed with water and brine, dried over anhydrous Na_2SO_4 , and evaporated under reduced pressure. The crude was purified by column chromatography
15 to give racemic *N*-(3-chloro-5-fluoro-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide (20 mg, 20%) as solid.

The racemic *N*-(3-chloro-5-fluoro-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide was subjected to chiral separation using Chiral Separation Method F. Second *N*-(3-chloro-5-fluoro-4-(oxazol-5-yl)phenyl)chroman-3-
20 carboxamide was eluted second at 5.25 min (21.6 mg).

Analytical HPLC Method C. Rt: 2.78 min; MS: 373.1 (M+H).

Compound (41): first *N*-(3-chloro-5-fluoro-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide



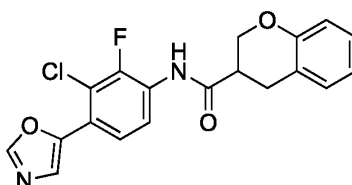
- 127 -

To a stirred solution of *N*-(4-bromo-3-chloro-2-fluorophenyl)chroman-3-carboxamide (100 mg, 0.260 mmol) in 1,4-dioxane/water (6 mL, 2:1) 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (66 mg, 0.338 mmol), and
5 Na₂CO₃ (55 mg, 0.521 mmol) were added under argon. The reaction mixture was degassed with argon for 20 min. Then Pd(dppf)Cl₂- dichloromethane complex (10.6 mg, 0.013 mmol) was added and degassed with argon for 5 min. The reaction mixture was sealed and stirred at 80°C for 8.0 h. The
10 reaction mixture was cooled to room temperature, diluted with water (5.0 mL), and extracted with EtOAc (2 x 30 mL). Organic layers were combined, washed with water and brine, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The crude was purified by column chromatography
15 to give racemic *N*-(3-chloro-5-fluoro-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide (20 mg, 20%) as solid.

The racemic *N*-(3-chloro-5-fluoro-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide was subjected to chiral separation using Chiral Separation Method F. First *N*-(3-chloro-5-fluoro-4-(oxazol-5-yl)phenyl)chroman-3-
20 carboxamide was eluted first at 4.78 min (21.9 mg).

Analytical HPLC Method C. Rt: 2.78 min; MS: 373.1 (M+H).

Compound (42): *N*-(3-chloro-2-fluoro-4-(oxazol-5-yl)phenyl)chromane-3-carboxamide



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To a stirred solution of N-(4-bromo-3-chloro-2-fluorophenyl)chroman-3-carboxamide (100 mg, 0.260 mmol) in 1,4-dioxane/water (6 mL, 2:1) 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (66 mg, 0.338 mmol), and
5 Na₂CO₃ (55 mg, 0.521 mmol) were added under argon. The reaction mixture was degassed with argon for 20 min. Then Pd(dppf)Cl₂- dichloromethane complex (10.63 mg, 0.013 mmol) was added and degassed with argon for 5 min. The reaction mixture was sealed and stirred at 80° C for 8 h.
10 The reaction mixture was cooled to room temperature, diluted with water (5.0 mL), and extracted with ethyl acetate (2 x 30 mL). Organic layers were combined washed with water (10 mL) and brine (10 mL), dried over anhydrous sodium sulphate, and evaporated under reduced pressure.
15 The crude was purified by column chromatography to yield N-(3-chloro-2-fluoro-4-(oxazol-5-yl)phenyl)chroman-3-carboxamide (Compound 42) (19 mg, 19%) as solid.

Analytical HPLC Method C. Rt: 2.75 min; MS: 373.1 (M+H).