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(54) Benevnelse **MIRABEGRON FOR THE TREATMENT OF RETINAL DISEASES**

(56) Anførte publikasjoner

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JENA J. STEINLE ET AL: "[beta] 3 -Adrenergic Receptors Regulate Retinal Endothelial Cell Migration and Proliferation", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 278, no. 23, 6 juin 2003 (2003-06-06) , pages 20681-20686, XP055274900, US ISSN: 0021-9258, DOI: 10.1074/jbc.M300368200
STEINLE J J ET AL: "beta3-Adrenergic receptors mediate choroidal endothelial cell invasion, proliferation, and cell elongation", EXPERIMENTAL EYE RESEARCH, ACADEMIC PRESS LTD, LONDON, vol. 80, no. 1, 1 janvier 2005 (2005-01-01), pages 83-91, XP004712453, ISSN: 0014-4835, DOI: 10.1016/J.EXER.2004.08.015

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# Mirabegron for treatment of retinal diseases

## FIELD OF THE INVENTION

This application concerns the treatment of retinal diseases, such as age-related macular degeneration. This application in particular concerns the use of mirabegron or one of its analogues, salts or solvates for the treatment of a retinal disease, in particular for the treatment of age-related macular degeneration.

## PRIOR ART

Age-related macular degeneration (AMD) is a major cause of blindness (in the legal sense) in developed countries, and the most prevalent ocular disorder among the elderly. AMD is characterised by a degeneration of the neuroepithelium in the macular area of the eye. Two major forms of advanced stage AMD can be distinguished: neovascular AMD and atrophic AMD.

Neovascular AMD, so-called moist or exudative AMD, is reflected in a proliferation of new abnormal blood vessels beneath the retina. This phenomenon is called “choroidal neovascularisation” or “CNV”. These new fragile vessels allow serum that is responsible for lifting the retina, and/or blood, to diffuse, giving rise to a retinal haemorrhage. The neovascular AMD is the major cause of blindness in elderly people in industrialised countries. A number of treatments have been developed to improve the clinical situation of patients, in particular therapies targeting VEGFA, a powerful stimulator of angiogenesis, and vascular permeability.

The atrophic AMD, also known as geographic atrophy or dry AMD, corresponds to the progressive disappearance of the cells of the retinal pigment epithelium (RPE), then those of the photoreceptors located at the level of the macula. This process generates holes of increasing size in the macula, visible by simply observing the retina (fundus oculi).

The incidence of neovascular AMD and atrophic AMD is comparable, but the 'expansion of atrophic lesions and associated visual disorders are generally slower in the case of atrophic AMD. It usually takes between five and ten years before the patient loses his central vision. No approved therapy for preventing or treating atrophic AMD currently exists, principally because of it not being possible to identify the target molecules. Some studies have shown that the intake of

Vitamins E and C, beta carotenoids and zinc could slow down the development of atrophic AMD. However, the progression of the disease is not halted.

Studies have shown that the accumulation of lipofusion, a cellular pigment composed of molecule debris, in the cells of the RPE, is a symptom associated with the atrophic form of AMD (Nandakumar et al., Seminars in Ophthalmology. 2012, 27(5-6):197-201; Schmitz-Valckenberg et al., Survey of Ophthalmology. 2009.54(1): 96-117). A deficiency in digestion of external segments of photoreceptors by RPE is the cause of said accumulation, and is probably linked to decreased activity of the lysosomal enzymes (Mahon et al., Curr Eye Res. 2004, 28:277-284). Actually, the activity of the lysosomal enzymes assumes its maximum value in a very acidic pH range. An increase in the lysosomal pH of the RPE cells thus reduces this digestive process, which is indispensable to good retinal functioning.

The international patent application WO 2008/042399 describes a method of treating AMD by restoring an acid lysosomal pH. This patent application likewise describes that stimulating adenosine or beta-adrenergic receptors could decrease the lysosomal pH.

However, the Applicant has shown that certain molecules, such as those known to enhance the beta-adrenergic receptors, although they reduce the lysosomal pH of the RPE cells, do not induce the digestion of the external segments of photoreceptors (*cf*. the Examples) and thus do not make it possible to treat AMD.

Furthermore, no molecule has yet been clinically validated, as at the present time.

Thus, there is always a need to identify the molecules ensuring optimal lysosomal activity, in order to enable degradation of external segments of photoreceptors in the RPE cells, thus making it possible to prevent and/or treat the AMD.

The Applicant has demonstrated, in a surprising manner, that some adrenergic receptor agonists, such as the mirabegron, significantly reduce the accumulation of lipofuscin in the RPE cells.

The present invention thus concerns the use of mirabegron or one of its salts or solvates for the treatment of a retinal disease, such as age-related macular degeneration.

## SUMMARY

The present invention concerns an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of a retinal disease affecting the macula in a subject.

In one embodiment, said (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide is the mirabegron, a pharmaceutically acceptable salt or a solvate thereof.

In a particular embodiment, said retinal disease is age-related macular degeneration, preferably age-related macular degeneration of the atrophic type.

The present invention likewise concerns a pharmaceutical composition comprising an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or a pharmaceutically acceptable salt or solvate thereof for the use of it, such as is described above, and at least one pharmaceutically acceptable vehicle.

The present invention moreover concerns a medicament comprising an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or a pharmaceutically acceptable salt or solvate thereof for use of it as described above.

In one embodiment, said pharmaceutical composition or medicament in accordance with the invention is intended to be administered to the subject who needs it orally or topically.

The present invention likewise concerns a kit, comprising a compound, a pharmaceutical composition or medicament of the kind described above.

In one embodiment, said kit is characterised in that it further comprises an apparatus for administering said compound, pharmaceutical composition or medicament to a subject in need of it, and optionally the instructions for administering said compound, pharmaceutical composition or medicament to said subject.

The present invention moreover concerns mirabegron for use for the treatment of AMD.

## DEFINITIONS

The terms above are defined, in the present invention, in the following manner:

- A "**pharmaceutically acceptable salt**" of the compound of the invention includes the salts added to an acid or a base of said compound. Suitable acid addition salts are formed from the acids forming the non-toxic salts. Examples of salts added to an acid include, but are not limited to, acetate salts, trifluoroacetate salts, adipate salts, aspartate salts, benzoate salts, besylate salts, bicarbonate/carbonate salts, bisulphate/sulphate salts, borate salts, tetrafluoroborate, camsylate salts, citrate salts, cyclamate salts, edisylate salts, esylate salts, formate salts, fumarate salts, gluceptate salts, gluconate salts, glucuronate salts, hexafluorophosphate salts, hibenzate salts, hydrochloride/chloride salts, hydrobromide/bromide salts, hydroiodide/iodide salts, isethionate salts, lactate salts, malate salts, maleate salts, malonate salts, mesylate salts, methyl sulphate salts, naphthylate salts, 2-napsylate salts, nicotinate salts, nitrate salts, orotate salts, oxalate salts, palmitate salts, pamoate salts, phosphate/hydrogen phosphate/dihydrogen phosphate salts, pyroglutamate salts, saccharate salts, stearate salts, succinate salts, tannate salts, tartrate salts, tosylate, trifluoroacetate and xinofoate salts. Suitable base addition salts are formed from the bases forming the non-toxic salts. Some examples of salts added to a base include, but are not limited to, aluminium salts, arginine salts, benzathine salts, calcium salts, choline salts, diethylamine salts, diolamine salts, glycine salts, lysine salts, magnesium salts, meglumine, olamine salts, potassium salts, sodium salts, tromethamine salts, 2-(diethylamino)ethanol salts, ethanolamine salts, morpholine salts, 4- (2-hydroxyethyl)morpholine salts and zinc salts. Pharmaceutically acceptable salts preferably include hydrochloride/chloride, hydrobromide/bromide, bisulphate/sulphate, nitrate, citrate, and acetate.

- The term "**solvate**" is used in the present invention to describe a compound of the invention comprising stoichiometric or substoichiometric amounts of one or more of a pharmaceutically acceptable solvent molecule, such as ethanol.

- The term "**subject**" concerns a mammal, preferably a human being. In one embodiment, the subject may be a "patient", i.e. a warm-blooded animal, preferably a human being, awaiting or receiving medical attention, who has been the subject of a medical procedure, or who is being monitored for the development of a retinal disease. In one embodiment, the subject is an adult, for example a subject over the age of 18 years. In another

embodiment, the subject is a child, for example a subject under 18 years of age. In one embodiment, the subject is a man. In another embodiment, the subject is a woman.

- The terms "**treatment**" or "**to treat**" simultaneously concern the therapeutic treatment and the prophylactic or preventive measures, the object of which is to prevent or slow down the progression of a retinal disease. The subjects who are in need of treatment include those who already have a retinal disease, those with a predisposition towards developing a retinal disease, and those in the case of whom a retinal disease needs to be prevented. A subject is successfully treated for a retinal disease if, after having received a therapeutically effective amount of a compound of the invention, the patient shows an observable or measurable reduction, or the absence of, at least one of the following points: a reduction in the number of pathogenic cells, a reduction in the percentage of pathogenic cells in comparison to the total number of cells, and/or of one or more of the symptoms associated with the retinal disease, an improvement in visual acuity or an improvement in the quality of life. The evaluation parameters above can easily be measured using the routine procedures with which a doctor is familiar.

- The term "**vehicle**" concerns a substance which carries the product of interest in a composition, which may, in particular, be a substance which allows it to dissolve. The vehicle may, for example, be water.

- A "**pharmaceutically acceptable vehicle**" concerns a vehicle which does not produce an adverse, allergic or undesirable reaction when it is administered to a subject. That includes all the solvents, dispersion media, coatings, antibacterial and anti-fungal agents, isotonic agents, delayed absorption agents and other similar substances. To be administered to a human being, the preparations need to respond to the criteria of sterility, pyrogenicity, and general standards of safety and purity stipulated by the regulatory agencies, such as the FDA or the EMA.

- A "**therapeutically effective amount**" concerns the amount o the therapeutic agent that is necessary and sufficient, without causing significant negative or undesirable effects, to (1) retard or prevent the appearance of the retinal disease ; (2) decrease or halt the progression or aggravation of, or deterioration in, one or more of the symptoms of the retinal disease; (3) relieve, or bring about improvements in, the symptoms of the retinal disease; (4) reduce the severity or incidence of the retinal disease, and/or (5) cure the retinal disease. A

therapeutically effective amount can be administered prior to the appearance of the retinal disease, for preventive or prophylactic action. Alternatively or additionally, the therapeutically effective amount can be administered prior to the initiation of the retinal disease, for therapeutic action.

- "**Approximately**", placed in front of a number, means give or take 10% of the nominal value of said number.

**DETAILED DESCRIPTION**

This application concerns the use of a compound to treat a retinal disease in a subject who is in need of it, said compound being an adrenergic receptor agonist.

Preferably, in one embodiment, the compound of the invention is an adrenergic receptor agonist, beta 1, 2 or 3, preferably beta 3.

In one embodiment, the compound of the invention is an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or an analogue, or a pharmaceutically acceptable salt or solvate thereof.

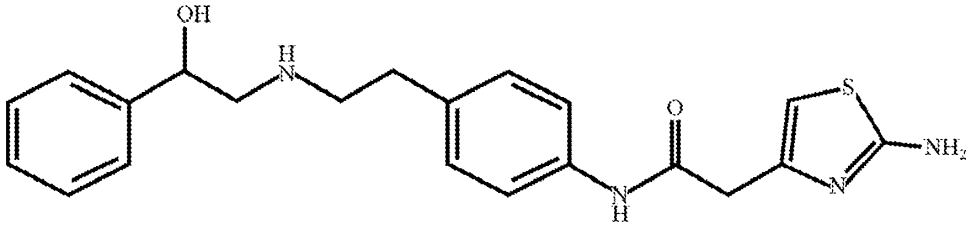
In this document, said (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide is also referred to by the term "mirabegron".

Thus, the compound of the invention is mirabegron.

The Applicant has in particular demonstrated that the mirabegron reduces the lysosomal pH at a low concentration (1 pM, *cf*. the Examples and Figure 1). The Applicant has, moreover, evidenced that mirabegron restores the activity of cathepsin D, a lysosomal proteolytic enzyme, in a significant manner, requiring an acid pH for its activity (*cf*. the Examples and Figure 2). These results have been confirmed in a lipofuscin accumulation cell model. Actually, the Applicant has demonstrated that the mirabegron reduces the accumulation of lipofuscin after two weeks of treatment (*cf*. the Examples and Figure 3). Thus, the Applicant has demonstrated the therapeutic potential of this molecule for treating AMD.

The application therefore concerns the mirabegron or an analogue or a pharmaceutically acceptable salt or solvate thereof for the use of it in the treatment of a retinal disease.

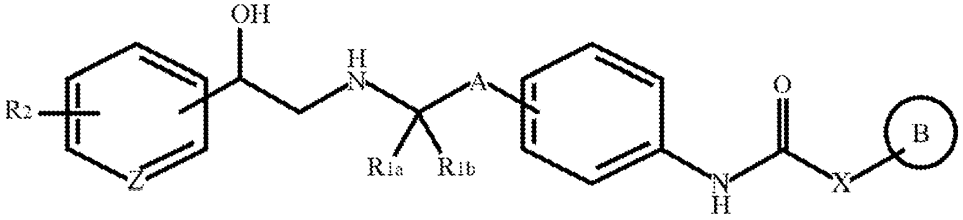
The mirabegron has the following general formula:



The mirabegron likewise goes under the name of Betmiga™, Betanis™ or Myrabetriq™.

Some examples of analogues of mirabegron include, without being limited to, the compounds described in the patent US6346532.

Thus, an analogue of the mirabegron has the following general formula (I):



wherein:

- The B-ring represents a heteroaryl group, which may be substituted and can be fused with a benzene ring;
- X represents a bond, a lower alkylene or a lower alkenylene, which may be substituted by a hydroxyl group or a lower alkyl group, a carbonyl, or a group represented by - NH - (when X is a lower alkylene group which may be substituted by a lower alkyl group, the carbon-bound hydrogen atoms constituting the B-ring may form a lower alkylene group with the lower alkyl group, thus forming a ring);
- A represents a lower alkylene or a group represented by -lower alkylene-O-;
- R1a and R2a may be identical or different, each one representing a hydrogen atom or a lower alkyl group;
- R2 represents a hydrogen atom or a halogen atom; and
- Z represents a nitrogen atom or a group represented by =CH-.

In the present document, the term “lower” means a linear or branched hydrocarbon chain having from 1 to 6 carbon atoms, unless otherwise specified.

Examples of a “lower alkyl group” include, but are not limited to, methyl, ethyl, linear or branched propyl, linear or branched butyl, linear or branched pentyl, and linear or branched hexyl. The lower alkyl group is preferably an alkyl having between 1 and 4 carbon atoms, and in particular methyl, ethyl, propyl and isopropyl.

A non-exhaustive example of a “lower alkylene group” is a bivalent group obtained by subtracting an arbitrary number of hydrogen atoms from the “lower alkyl group” defined above, preferably an alkylene group having 1 to 4 carbon atoms, and in particular methylene, ethylene, propylene and butylene.

Examples of a “lower alkenylene group” include, but are not limited to, the vinylene, propenylene, butenylene, pentenylene and hexenylene groups.

In the present document, the “heteroaryl group that can be fused with a benzene ring” in the “heteroaryl group that can be substituted or that can be fused with a benzene ring” means a ring group in which the benzene ring is fused with a heteroaryl group, as described below, or an unfused heteroaryl group.

Examples of a “ring group in which the benzene ring is fused with a heteroaryl group” include, but are not limited to, quinolyl, isoquinolyl, quinazolinyl, quinolidinyl, quinoxalinyl, cinnolinyl, benzimidazolyl, imidazopyridyl, benzofuranyl, benzoisoxazolyl, benzoxazolyl, benzothiazolyl, oxazolopyridyl, isothiazolopyridyl and benzothiazolyl; and the additional oxygen rings, such as oxobenzofurayl.

Examples of an “unfused heteroaryl group” include, but are not limited to, monocyclic heteroaryl groups, such as furyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, pyrazolyl, isothiazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, thiadiazolyl, triazolyl and tetrazolyl; and the bicyclic heteroaryl groups, such as naphthyridinyl and pyridopyrimidinyl.

The substituent in the “heteroaryl group that can be substituted and that can be fused with a benzene ring”, can be any group usually substituted in this cyclic group. Examples include, but are not limited to, a halogen atom, a lower alkyl, a lower alkenyl, a lower alkynyl, a hydroxyl

group, sulfanyl, a lower halogenoalkyl, lower alkyl-O-, lower alkyl-S-, lower alkyl-O-CO-, carboxy, sulfonyl, sulfinyl, lower alkyl-SO-, lower alkyl-$SO_2$-, lower alkyl-CO-, lower alkyl-CO-O-, lower alkyl carbamoyl -NH-CO-, lower di-alkyl-N-CO-, nitro, cyano, amino, guanidino, lower alkyl-CO-NH-,lower alkyl-$SO_2$-NH-, lower alkyl-NH-, lower di-alkyl-N-, O-lower alkylene-O- and other similar groups.

These substituents may, in turn, be substituted by a substituent such as an aryl group, a heteroaryl group, a halogen atom, a hydroxyl group, sulfanyl, a lower halogenoalkyl, lower alkyl-O-, lower alkyl-S-, lower alkyl-O-CO-, carboxy, sulfonyl, sulfinyl, lower alkyl-SO-, lower alkyl-$SO_2$-, lower alkyl-CO-, lower alkyl-CO-O-, carbamoyl, lower alkyl-NH-CO-, lower di-alkyl-N-CO-, nitro, cyano, amino, guanidino, lower alkyl-CO-NH-, lower alkyl-$SO_2$-NH-, lower alkyl-NH-, lower di-alkyl-N-, and other similar groups. These substituents, such as an aryl group, a heteroaryl group or other group, may, in turn, be substituted by a halogen atom, etc. ...

The “lower alkenyl group” is a linear or branched alkenyl group having 2 to 6 carbon atoms. Examples include, but are not limited to vinyl, propenyl, butenyl, pentenyl and hexenyl.

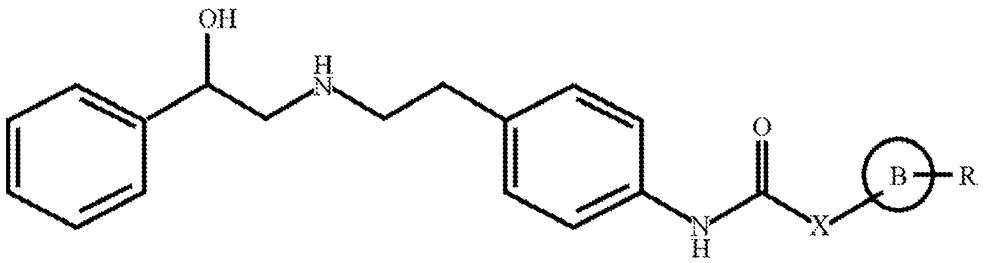
The “lower alkynyl group” is a linear or branched alkynyl group having 2 to 6 carbon atoms. Examples include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl and hexynyl.

The term “halogen atom” means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom. The term “lower halogenoalkyl group” means a group in which one (of the) hydrogen atom(s) in the alkyl group described above, arbitrarily chosen, is (are) substituted by one (of the) halogen atom(s).

The case in which X is a bond means that the carbon atom in the CO-group is directly linked to the B-ring.

The compound in accordance with the application, preferably mirabegron or an analogue, comprises at least one asymmetric carbon atom. Hence, optical isomers exist, such as the configuration (R) or (S) compounds, the racemates, the diastereoisomers, etc. ... The present invention includes all the isomers, each of the isolated isomers and their mixtures. The present invention likewise includes the hydrates, solvates (such as the ethanol solvates) and the polymorphic substances of the compound of the invention, the mirabegron or one of its analogues.

In one embodiment, the analogue of the mirabegron has the following general formula (Ia):




wherein:

- the B-ring represents a heteroaryl group;
- X represents a bond or a lower alkylene group;
- R represents a hydrogen atom, a halogen atom, a lower alkylene group, a nitrogen group, a lower alkyl aryl group or a lower aryl halogenoalkyl group, or a salt thereof.

In one embodiment, the analogue of the mirabegron is selected from among the group comprising (R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl] -2-pyridinecarboxyanilide, (R)-2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-acetanilide, (R)-2-[1-(3,4-dichlorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide, (R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide, (R)-2-(2-benzyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino]ethyl]acetanilide, (R)-2-(2-aminopyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino]ethyl)-2-(2-pyrazinyl)acetanilide, and (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl)-2-(2-pyrimidinyl)-acetanilide, or one of their salts.

In one embodiment, the (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or an analogue, a salt or a pharmaceutically acceptable solvate thereof is not in heavy or deuterated form. In a particular embodiment, the mirabegron is non-deuterated.

In one embodiment, the mirabegron is in crystalline form. In a particular embodiment, the mirabegron is in alpha-crystalline form. In another particular embodiment, the mirabegron is in beta-crystalline form. The alpha and beta crystalline forms of the mirabegron are with a free base, and have specific physicochemical properties. The alpha and beta crystalline forms of the mirabegron are described in the patent US7342117.

In the present document, the term “retinal disease” encompasses the different disorders which may affect the retina, which is the layer of nerve cells covering the back of the eye.

Examples of disorders affecting the retina include, but are not limited to, age-related macular degeneration (AMD), Stargardt's disease, diabetic retinopathy and retinitis pigmentosa.

According to the invention, the retinal disease is a disease which affects the macula, i.e. the central area of the retina. Examples of diseases affecting the macular include, but are not limited to, age-related macular degeneration and Stargardt's disease.

According to one embodiment, the retinal disease pertaining to the invention is age-related macular degeneration or Stargardt's disease.

In one embodiment, the retinal disease pertaining to the invention is age-related macular degeneration.

In one embodiment, the age-related macular degeneration in accordance with the invention is at an early stage, likewise known as age-related maculopathy. The early stage age-related macular degeneration is characterised by the accumulation in and around the macula of waste from the functioning of the photoreceptors (known as “drusen”), associated with pigment spots (alterations in the pigment epithelium).

In another embodiment, the age-related macular degeneration in accordance with the invention is at the late stage. The late stages are characterized by unilateral or bilateral complications. Two forms are then distinguished: the exudative and the atrophic form.

In one embodiment, the age-related macular degeneration is of the atrophic type, likewise known as dry AMD.

In another embodiment, the retinal disease relating to the invention is Stargardt's disease. Stargardt's disease is a hereditary form of macular dystrophy, which is generally manifest among children between 7 and 12 years of age.

In one embodiment, the subject is affected by a retinal disease, preferably AMD or Stargardt's disease. In one embodiment, the subject is affected by AMD at an early stage. In a further embodiment, the subject is affected by AMD at a late stage.

In a further embodiment, the subject is susceptible to being affected by a retinal disease, preferably AMD. In one embodiment, the subject is a subject who is at risk of developing retinal disease, according to the invention. Examples of risk include, but are not limited to, heredity (the present or past existence of other cases of retinal disease, preferably AMD, in the subject's family), the use of tobacco, being elderly, exposure to the sun, an unbalanced diet (for example, a low intake of green vegetables and omega-3 fatty acid), an elevated concentration of cholesterol in the blood, elevated blood pressure, and similar factors.

In one embodiment, the subject has not yet been treated with another treatment for the retinal disease in accordance with the invention. In another embodiment, the subject has already been treated with another treatment for the retinal disease in accordance with the invention. In one embodiment, the subject is a human being over the age of 45 years. In another embodiment, the subject is a human being under 18 years of age.

The present invention likewise concerns a composition comprising a compound in accordance with the invention.

In one embodiment, the composition of the invention comprises an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or a pharmaceutically acceptable salt or solvate thereof, preferably mirabegron.

In one embodiment, the composition of the invention is used for treating a retinal disease affecting the macula, preferably age-related macular degeneration.

The present invention moreover concerns a pharmaceutical composition comprising a compound of the invention and at least one pharmaceutically acceptable vehicle.

In one embodiment, the pharmaceutical composition of the invention comprises an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or a pharmaceutically acceptable salt or solvate thereof, preferably mirabegron, and at least one pharmaceutically acceptable vehicle.

In one embodiment, the pharmaceutical composition of the invention is used for treating a retinal disease affecting the macula, preferably age-related macular degeneration.

The present invention likewise concerns a medicament comprising a compound of the invention.

In one embodiment, the medicament of the invention comprises an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or a pharmaceutically acceptable salt or solvate thereof in accordance with the invention, preferably mirabegron, a composition or a pharmaceutical composition of the present invention.

In one embodiment, the medicament of the invention is used for treating a retinal disease affecting the macula, preferably age-related macular degeneration.

The composition, the pharmaceutical composition or the medicament of the present invention preferably comprise an effective therapeutic quantity of a compound of the invention, preferably an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or a pharmaceutically acceptable salt or solvate thereof, preferably mirabegron.

In one embodiment, the (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or a pharmaceutically acceptable salt or solvate thereof of the present invention, preferably mirabegron, is used in combination with at least one other therapeutic agent, to treat a retinal disease affecting the macula, preferably age-related macular degeneration.

Examples of other therapeutic agents for treating age-related macular degeneration include, but are not limited to, anti-vasoproliferative agents such as ranibizumab (Lucentis) or bevacizumab (Avastin), anti-angiogenic agents, such as the VEGF trap (Regeneron), bevasiranib or tyrosine kinase inhibitors.

In one embodiment, the therapeutically effective amount ranges from approximately 1 to 10,000 mg/mL of composition, pharmaceutical composition or medicament of the invention, preferably approximately 5 to approximately 5,000 mg/mL, preferably approximately 10 to approximately 2,000 mg/mL, preferably approximately 20 to approximately 100 mg/mL of composition, pharmaceutical composition or medicament of the invention.

In one embodiment, the therapeutically effective amount ranges from approximately 1 to 10,000 mg/g of composition, pharmaceutical composition or medicament of the invention, preferably approximately 5 to approximately 5,000 mg/g, preferably approximately 10 to approximately 2,000 mg/g, preferably approximately 20 to approximately 100 mg/g of composition, pharmaceutical composition or medicament of the invention.

It is understood that the total daily consumption of the (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or the analogue or the pharmaceutically acceptable salt or solvate thereof, preferably mirabegron, the composition, the pharmaceutical composition or the medicament of the invention will be adjusted by the doctor undertaking the treatment within the scope of his medical opinion. The therapeutically effective dose specific to each patient will depend upon a number of factors, including the disorder being treated and its severity; the activity of the compound used; the specific composition used; the patient's age, weight, general state of health, sex and diet, the duration and method of administration; the duration of the treatment; the medicaments used in combination or concurrently with the compound used, and other similar factors known in the medical field. For example, it is routine in this field to commence with doses of compounds below recommended doses, to await the therapeutic effect, and to gradually increase the dosage until the effect is achieved. The daily dosage of compounds may, however, vary considerably, from approximately 1 to approximately 10,000 mg per adult and day, preferably approximately 5 to approximately 5,000, preferably approximately 10 to approximately 2,000 mg, more preferably approximately 20 to approximately 100 mg per adult and day. Preferably, the composition comprises 1, 10, 20, 50, 100, 250, 500, 1,000 and 2,000 mg of the active ingredient for the symptomatic adjustment of the dosage to be administered to the patient who is to be treated. A medicament typically contains approximately 1 to approximately 10,000 mg of the active ingredient, preferably 5 to 5,000, preferably 10 to 2,000 mg of the active ingredient. An effective amount of the medicament is usually provided with one dose ranging from approximately 0.01 mg/kg to approximately 100 mg/kg of body weight per day, preferably approximately 0.05 mg/kg to approximately 40 mg/kg, preferably approximately 0.1 mg/kg to 20 mg/kg of body weight per day, more preferably from approximately 0.2 to approximately 1 mg/kg of body weight per day.

In one embodiment, the daily dose of the compound of the invention, preferably the mirabegron, the composition, the pharmaceutical composition or the medicament of the present invention is adjusted in line with the potential renal and/or hepatic disorders of the subject.

In one embodiment, the total daily dose of the (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or the analogue or the pharmaceutically acceptable salt or solvate thereof, preferably mirabegron, ranges from approx. 1 mg to approx. 100 mg, preferably approx. 10 mg to approx. 80 mg, preferably approx. 20 mg to approx. 60 mg.

In one particular embodiment, the initial total daily dose of the (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or the analogue or the pharmaceutically acceptable salt or solvate thereof, preferably mirabegron, ranges from approx. 10 mg to approx. 50 mg, preferably approx. 20 mg to approx. 30 mg, preferably approx. 25 mg. In another particular embodiment, the total daily maintenance dose of the (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or the analogue or the pharmaceutically acceptable salt or solvate thereof, preferably mirabegron, ranges from approx. 20 mg to approx. 80 mg, preferably approx. 40 mg to approx. 60 mg, preferably approx. 50 mg.

In one particular embodiment, the (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or the analogue or the pharmaceutically acceptable salt or solvate thereof, preferably mirabegron, the composition, the pharmaceutical composition or the medicament of the invention is administered at a dose of approx. 25 mg. In another particular embodiment, the (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or the analogue or the pharmaceutically acceptable salt or solvate thereof, preferably mirabegron, the composition, the pharmaceutical composition or the medicament of the invention is administered at a dose of approx. 50 mg.

In one embodiment, the medicament of the invention contains approx. 25 mg of the compound, the composition or the pharmaceutical composition of the invention. In another embodiment, the medicament of the invention contains approx. 50 mg of the compound, the composition or the pharmaceutical composition of the invention.

In one embodiment, the compound of the invention, preferably an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or the analogue or the pharmaceutically acceptable salt or solvate thereof, preferably mirabegron, the composition, the pharmaceutical composition or the medicament of the present invention, either on its own or in combination with another therapeutic agent, can be administered in the form of a unit dose, in admixture with conventional pharmaceutical supports, to animals or human beings. The

appropriate forms of uniform administration comprise oral forms of administration, such as tablets, capsules, powders, granules and suspensions or oral solutions, sublingual or intra-oral forms of administration, aerosols, implants, subcutaneous, transdermal, topical, intraperitoneal, intravenous, intrathecal, intraocular and intranasal forms of administration, as well as rectal forms of administration.

In one embodiment, the composition, pharmaceutical composition or medicament of the present invention comprises one or more pharmaceutically acceptable vehicles for a formulation adapted to oral administration.

Examples of forms adapted to oral administration include, but are not limited to, tablets (including extended release tablets), capsules, powders, granules, pills (including sugar-coated pills), capsules (including soft gelatin capsules), oral suspensions, drinkable solutions, and other similar forms.

In one embodiment, the composition, pharmaceutical composition or medicament of the present invention comprises one or more pharmaceutically acceptable vehicles for a formulation adapted to topical administration. In one particular embodiment, the composition, pharmaceutical composition or medicament of the present invention comprises one or more pharmaceutically acceptable vehicles for a formulation adapted to topical administration in the eye.

Examples of forms of the present invention adapted to topical administration include, but are not limited to, compositions in liquid, paste or solid form, and, more particularly, forms such as aqueous solutions, eye drops, droplets, dispersions, sprays or microcapsules, microparticles or nanoparticles or polymeric or gelatinised patches allowing for controlled release.

In one embodiment, the composition, pharmaceutical composition or medicament of the present invention comprises one or more pharmaceutically acceptable vehicles for a formulation suitable for injection. In one particular embodiment, the composition, pharmaceutical composition or medicament of the present invention has a form adapted for intraocular injection, preferably for an intravitreous injection.

Examples of forms of the present invention adapted to administration by way of injection include, but are not limited to, sterile aqueous solutions, dispersions, emulsions, suspensions, appropriate

solid forms for the preparation of solutions or suspensions through the addition of a liquid before use, such as powders, for example.

In one embodiment, the compound of the invention, preferably an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or the analogue or the pharmaceutically acceptable salt or solvate thereof, preferably mirabegron, the composition, the pharmaceutical composition or the medicament of the present invention, is administered to the subject at least once per day. For example, the compound, the composition, the pharmaceutical composition or the medicament of the invention may be administered once per day, twice per day or three times per day. The compound, the composition, the pharmaceutical composition or the medicament of the invention is preferably administered once per day.

In another embodiment, the compound of the invention, preferably an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or the analogue or the pharmaceutically acceptable salt or solvate thereof, preferably mirabegron, the composition, the pharmaceutical composition or the medicament of the present invention, is administered to the subject at least once per week. For example, the compound, the composition, the pharmaceutical composition or the medicament of the invention may be administered once per week, twice, three times, four times or up to seven times per week.

In another embodiment, the compound of the invention, preferably an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or the analogue or the pharmaceutically acceptable salt or solvate thereof, preferably mirabegron, the composition, the pharmaceutical composition or the medicament of the present invention, is administered to the subject at the most once per month. For example, the compound, the composition, the pharmaceutical composition or the medicament of the invention may be administered once per month, once every two months, once per calendar quarter, twice per year or once per year.

The present application likewise concerns a method of treating a retinal disease, preferably age-related macular degeneration, in a subject in need of it, comprising the administration vis-à-vis the subject of a therapeutically effective amount of a compound of the invention, as described above, preferably an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or an analogue or a pharmaceutically acceptable salt or solvate thereof, preferably mirabegron.

In one embodiment, the composition, pharmaceutical composition or medicament of the invention is administered to the subject.

The present application likewise concerns a method of reducing the lysosomal pH in the cells of the retinal pigment epithelium, comprising the administration of a composition comprising a compound of the invention, as described above, preferably an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or an analogue or a pharmaceutically acceptable salt or solvate thereof, preferably mirabegron.

The present application moreover concerns a method of increasing the digestion of external segments of the photoreceptors of the retinal pigment epithelium, comprising the administration of a composition comprising a compound of the invention, as described above, preferably an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or an analogue or a pharmaceutically acceptable salt or solvate thereof, preferably mirabegron.

The present application likewise concerns a method of reducing the accumulations of lipofuscin in the cells of the retinal pigment epithelium, comprising the administration of a composition, comprising a compound of the invention, as described above, preferably an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or an analogue or a pharmaceutically acceptable salt or solvate thereof, preferably mirabegron.

The present invention likewise concerns a kit comprising an (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or an analogue or a pharmaceutically acceptable salt or solvate thereof, a composition, a pharmaceutical composition or a medicament as described above.

According to one embodiment, the kit likewise comprises a device serving the purpose of administering the compound, the composition, the pharmaceutical composition or the medicament to a subject.

According to one embodiment, the kit moreover comprises instructions for administering the compound, the composition, the pharmaceutical composition or the medicament to said subject.

In one embodiment, the kit comprises an additional therapeutic agent. According to one embodiment, the additional therapeutic agent is another agent for treating the retinal disease in accordance with the invention.

In one embodiment, the additional therapeutic agent has a form adapted to the same method of administration as the compound, the composition, the pharmaceutical composition or the medicament of the invention. In another embodiment, the additional therapeutic agent has a form adapted to a different method of administration from that of the compound, the composition, the pharmaceutical composition or the medicament of the invention.

## BRIEF DESCRIPTION OF THE FIGURES

**Figure 1** is a histogram showing the effect of adrenergic receptor agonists, isoproterenol, mirabegron, amibegron and CL-316,243 upon the lysosomal pH of cells treated with tamoxifen. The results have been statistically compared using an Anova and a Dunnett's test. ****$p < 0.0001$, **$p < 0.01$.

**Figure 2** is a histogram showing the effect of adrenergic receptor agonistsagonists, mirabegron, isoproterenol, amibegron and CL-316,243 upon the activity of the cathepsin D of cells treated with concamycin.

**Figure 3** is a graph showing the intensity of autofluorescence of the lipofuscin after two weeks of co-treatment of the RPE cells by oxidised external segments and by the adrenergic receptor agonists amibegron,mirabegron, CL-316,243 and isoproterenol. Cells co-treated with oxidised external segments and DMSO serve as a control facility.

## EXAMPLES

The present invention will be understood better after reading the examples below, which illustrate the invention without limitation.

### Example 1

#### *Material and Methods*

*Primary culture of RPE of swine*

Pigs' eyes are delivered to the Vision Institute in a cold medium from a local abattoir. The eyes are dissected to remove the anterior segment of the eye, the vitreous and the neural retina. The eyeballs are then washed twice with PBS, filled with trypsin (0.25% in PBS) and incubated at 37°C for 1 hr. 15 mins. The RPE cells are then recovered by repeated pipetting, centrifuged in order to remove trypsin, and re-suspended in DMEM culture medium with the addition of 20% of foetal calf serum (DMEM20%SVF). The cells of each eye are then sown in a Petri dish that is 6 cm in diameter, cultivated in an atmosphere containing 5% CO2 at 37°C, and the culture medium changed after 24 hours and 4 days in vitro. After one week, the cells reach the confluence and can then be passed.

***Alkalinisation and lysosomal pH ($pH_L$) measurement of RPE***

After a week in culture, cells are treated with trypsin and transferred into a tray 96 with holes and a black background at a cell density of 1.5 x $10^5$ cells/$cm^2$ in some DMEM2%SVF. After 24 hours, the cells are treated with a beta-adrenergic agonist (mirabegron, amibegron, clenbuterol or isoproterenol at 1 pM or CL-316,243 at 20 nM), and 5 minutes later with tamoxifen (15 µM), and the $pH_L$is measured after 20 more minutes. Said measurement is implemented using a coloured indicator (Lysosensor Yellow/BlueDND-160) presenting an excitability at 329 and 384 nm, and enabling variations in pH to be measured in acidic organelles, irrespective of the concentration of the colouring agent. In order to implement the measurement of the $pH_L$, the cells are incubated by the colouring agent for 5 minutes at 37°C, and the fluorescence emitted by the dye is measured on a plate reader. The ratio of excited light to 329/384 nm is then converted to pH using a calibration range (pH 4 to pH 6) carried out in a KCl buffer in the presence of 10 µM of monensin and 20 µM of nigericin, two ionophores.

***Measuring cathepsin D activity***

After a week in culture, cells are treated with trypsin and transferred into Petri dishes that are 3.5 cm in diameter at a cell density of 1.5 x $10^5$ cells/$cm^2$ in some DMEM2%SVF. After 24 hours, the cells are treated with 20 nM of concamycin in order to inhibit the activity of the cathepsin D, as well as with a beta-adrenergic agonist. Following 24 hours of treatment, the cells are washed using some PBS, then transferred to an ice extraction buffer. The cell extract is centrifuged at 2,000 rpm at 4°C for 10 minutes and the supernatant corresponding to the cytosolic part is frozen at -80°C until the enzymatic activity is measured. The activity of the cathepsin D is measured using the method of Anson (J Gen Physiol. 1938, 22(1): 79-89) that we have adapted to our experimental

design. In summary, the cytosolic extract is incubated for 10 minutes at 37°C in a haemoglobin solution (2.5% in 400 mM of citrate buffer at pH 2.8). The reaction is halted by adding 5% trichloroacetic acid, and the mixture is centrifuged. The optical density of the supernatant containing the degradate of the haemoglobin is measured at 280 nm. The absorbency is corrected by subtracting that of the control, prepared as previously, but adding the haemoglobin after having stopped the enzymatic reaction. A unit of cathepsin D is then defined as being the quantity of enzyme necessary in order to bring about a change in absorbency of 1 to 280 nm for 60 minutes of incubation using the experimental conditions described above. The protein concentration of the cell lysates is measured in accordance with the method of Bradford, in order to normalise the results.

***Preparation of external segments of swine photoreceptors (ESP)***

Pig retinas are collected in a dark room under red light. The ESPs are separated from the sucrose gradient retinas, as described below. In summary, the pig retinas are homogenised in a solution containing 20% sucrose, 20 mM of tris-acetate pH 7.2, 2 mM of MgCl2, 10 mM of glucose and 5 mM of taurine. The samples are then deposited on a continuous sucrose gradient (25 at 60%) containing 20 mM of tris-acetate at pH 7.2, 10 mM of glucose and 5 mM of taurine, and centrifuged at 25,000 rpm at 4°C for 2 hrs. The pink stripes obtained correspond to the ESP, and are then sampled and subsequently frozen at -80°C until they are used.

In order to obtain the oxidised ESPs (ESP-ox), the ESPs are exposed to ultra-violet light ($\lambda$=312 nm) for 3 hrs. They are then washed in some PBS, centrifuged at 5,000 rpm, and suspended again in some DMEM20%FCS containing 2.5% sucrose.

***In vitro model of lipofuscin accumulation in the RPE***

After a week in culture, cells are treated with trypsin and transferred into a tray 96 with holes and a pale background at a cell density of 1.5 x $10^5$ cells/$cm^2$ in some DMEM2%SVF.

In order to induce an accumulation of material of the lipofuscin type into the RPE cells, the latter are treated 3 times per week using 5x$10^6$ ESP-ox in some DMEM20%FCS containing 2.5% sucrose for two weeks. In parallel, the cells are treated, or not, using a beta-adrenergic antagonist. The autofluorescence induced by the accumulation of lipofuscin is measured using a plate reader

(excitation at 480 nm and emission between 500 and 700 nm corresponding to the emission spectrum of the lipofuscin).

***Results***

*Effect of the agonists on the lysosomal pH*

The molecules tested in experiments consist of three specific beta-3 adrenergic receptor agonists (mirabegron, amibegron, CL-316,243), and an unspecified agonist (isoproterenol).

These molecules have been tested in an alkalisation cell model of the lysosomal pH of the RPE induiced by the cells being treated using 15 µM of tamoxifen and causing an increase in the pH in the order of 1 pH unit in 20 minutes.

All the molecules tested have made it possible to obtain a maximum effect of close to 50% on the re-acidification of the pH at 1 pM, with the exception of the CL-316,243, effective as from 20 nM (Figure 1).

***Effect of the agonists on the activity of cathepsin D***

The cathepsin D is the predominantly lysosomal proteolytic enzyme present in the retinal pigment epithelium participating in the digestion of external segments of the photoreceptors. Its activity depends on the protonation of the aspartic amino acid of its active site and its conformation, both of which require an acidic environment. Thus, the study of the effect of the molecules tested on the activity of the cathepsin D makes it possible to determine the effect of these molecules on the activity of the lysosomal enzymes.

With the exception of the amibegron, the treatment of the RPE cells with all the molecules tested makes it possible to partially restore the activity of the cathepsin D (Figure 2). In particular, the treatment using mirabegron makes the activity of the enzyme three times as effective (0.040 unit/ml of enzyme/min/µg of protein) compared to the negative control which constitutes the treatment using concanamycin (0.013 units/ml of enzyme/min/µg of protein).

*Effect of the agonists on the accumulations of lipofuscin in the RPE*

In order to verify if the different beta-adrenergic agonists are likewise capable of acting upon the accumulation of lipofuscin, we have tested them in a cell model in which said accumulation is induced by treating RPE cells with oxidised ES through exposure to ultra-violet radiation every other day. The agonists were added to the culture medium at 10 µM at the time of the treatments with ES. The accumulation of lipofuscin was measured after two weeks of co-treatment by measuring the autofluorescence of the cells.

The results show that in two weeks only the mirabegron is capable of reducing close to 20% of the lipofuscin accumulation by RPE cells (Figure 3).

Patentkrav

1. (R)-2-(2-aminotiazol-4-yl)-4'-[2-[(2-hydroksy-2-fenyletyl)amino]etyl]eddiksyreanilid eller et farmasøytisk akseptabelt salt eller solvat derav for anvendelse i behandlingen av en netthinnesykdom hos et individ, (R)-2-(2-aminotiazol-4-yl)-4'-[2-[(2-hydroksy-2-fenyletyl)amino]etyl]eddiksyreanilidet er mirabegron, et farmasøytisk akseptabelt salt eller solvat derav, og hvori netthinnesykdommen er en sykdom som påvirker makulaen.

2. (R)-2-(2-aminotiazol-4-yl)-4'-[2-[(2-hydroksy-2-fenyletyl)amino]etyl]eddiksyreanilid eller et farmasøytisk akseptabelt salt eller solvat derav for anvendelse ifølge krav 1, hvori netthinnesykdommen er aldersrelatert makuladegenerasjon, fortrinnsvis atrofisk aldersrelatert makuladegenerasjon.

3. Farmasøytisk sammensetning omfattende et (R)-2-(2-aminotiazol-4-yl)-4'-[2-[(2-hydroksy-2-fenyletyl)amino]etyl]eddiksyreanilid eller et farmasøytisk akseptabelt salt eller solvat derav for anvendelse ifølge et hvilket som helst av kravene 1 til 2 og minst én farmasøytisk akseptabel bærer.

4. Medikament omfattende et (R)-2-(2-aminotiazol-4-yl)-4'-[2-[(2-hydroksy-2-fenyletyl)amino]etyl]eddiksyreanilid eller et farmasøytisk akseptabelt salt eller solvat derav for anvendelse ifølge et hvilket som helst av kravene 1 til 2.

5. Farmasøytisk sammensetning eller medikament for anvendelse ifølge et hvilket som helst av kravene 3 eller 4, karakterisert ved at den er ment å administreres til individet med behov derav oralt eller topisk.

6. Sett omfattende en forbindelse for anvendelse ifølge et hvilket som helst av kravene 1 til 2, en farmasøytisk sammensetning for anvendelse ifølge et hvilket som helst av kravene 3 og 5, eller et medikament for anvendelse ifølge et hvilket som helst av kravene 4 og 5.

7. Sett for anvendelse ifølge krav 6, karakterisert ved at det videre omfatter et apparat for administrering av forbindelsen, farmasøytisk sammensetning eller medikament til et individ med behov derav, og eventuelt instruksjonene for administrering av forbindelsen, farmasøytisk sammensetning eller medikament til individet.

8. Mirabegron for anvendelse for behandling av AMD.

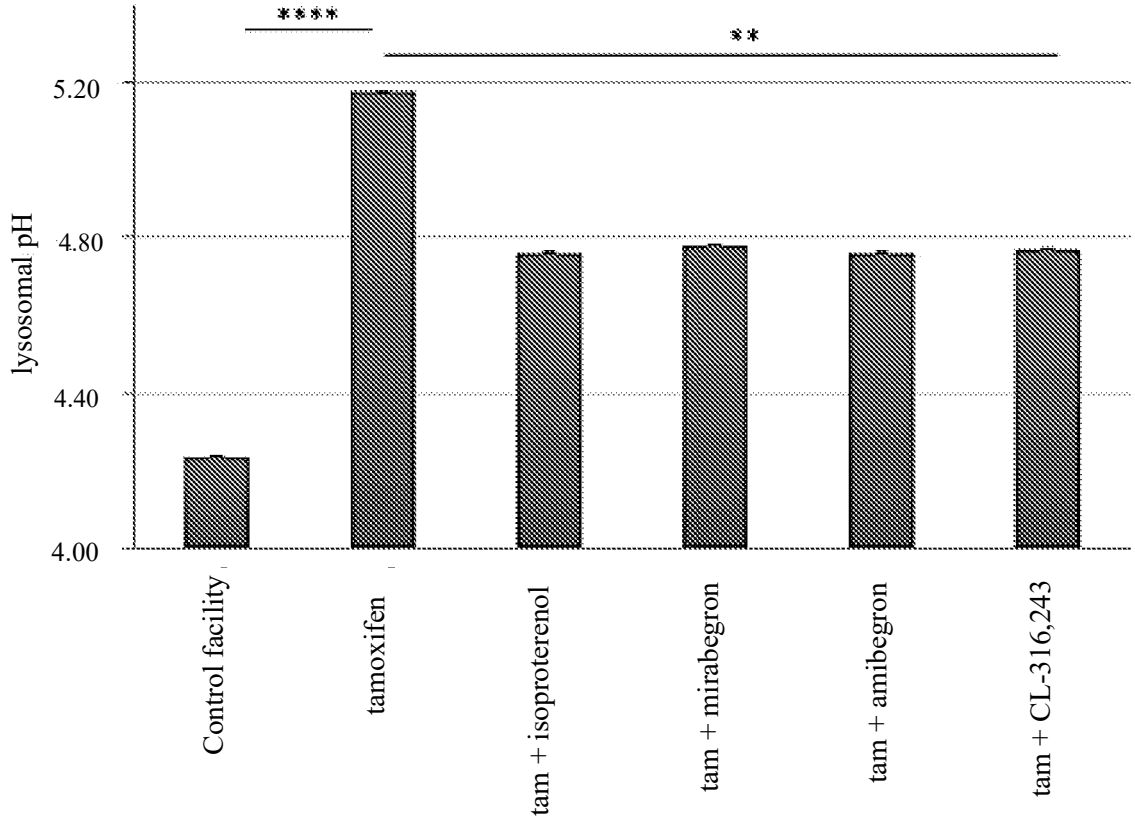

****
**
5.20
4.80
4.40
4.00
lysosomal pH
Control facility
tamoxifen
tam + isoproterenol
tam + mirabegron
tam + amibegron
tam + CL-316,243

FIG. 1

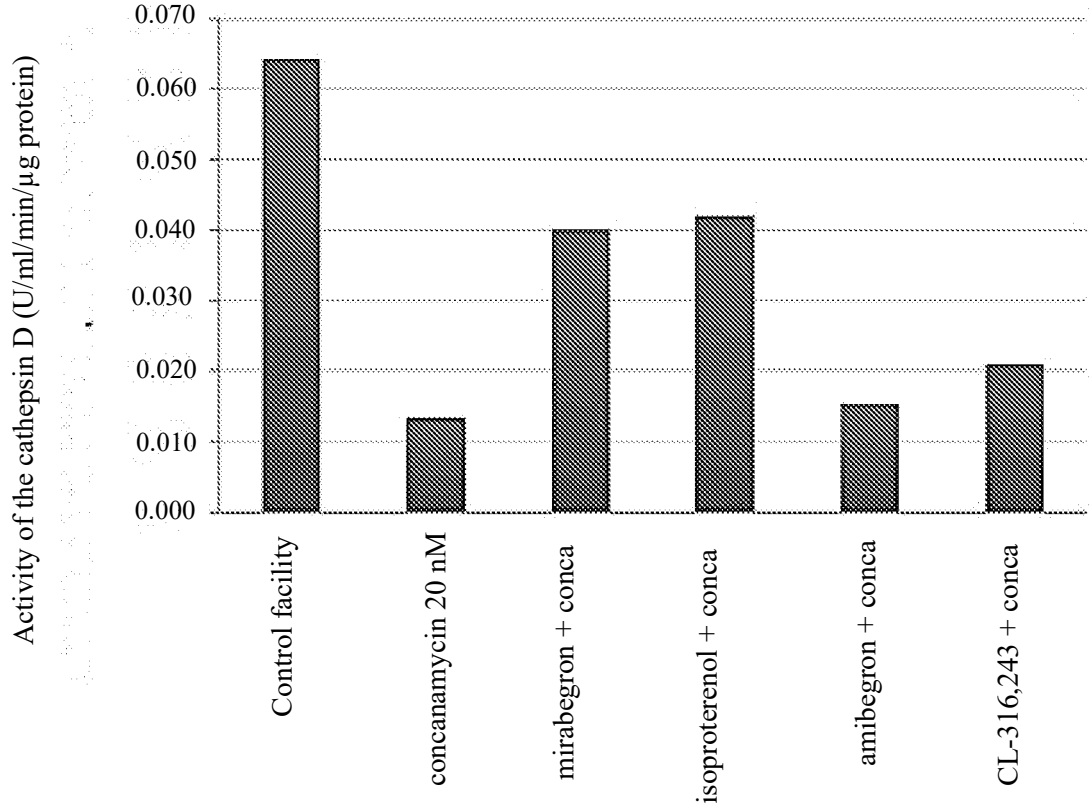

0.070
0.060
0.050
0.040
0.030
0.020
0.010
0.000
Activity of the cathepsin D (U/ml/min/µg protein)
Control facility
concanamycin 20 nM
mirabegron + conca
isoproterenol + conca
amibegron + conca
CL-316,243 + conca

FIG. 2

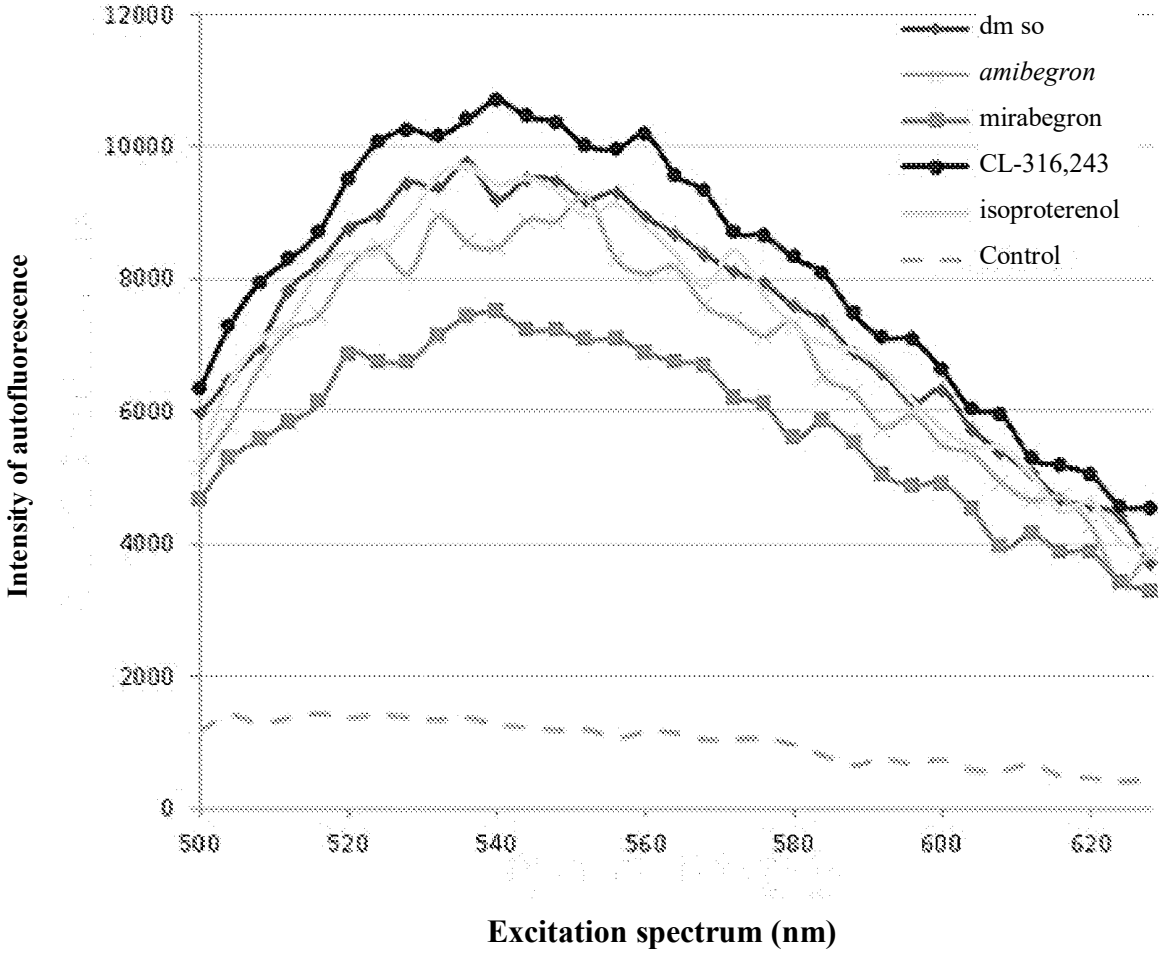

12000
10000
8000
6000
4000
2000
0
500
520
540
560
580
600
620
dm so
amibegron
mirabegron
CL-316,243
isoproterenol
Control
Intensity of autofluorescence
Excitation spectrum (nm)

FIG. 3