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(54) Benævnelse: **ESTER-PRO-DRUGS AF [3-(1-(1H-IMIDAZOL-4-YL)ETHYL)-2-METHYLPHENYL] METHANOL TIL BEHANDLING AF NETHINDESYGDOMME**

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DESCRIPTION

BACKGROUND OF THE INVENTION

1. Field of the invention

[0001] The present invention relates to a composition for use in a method for treating retinal diseases in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising ester pro-drugs of [3-(1-(1H-imidazol-4-yl)ethyl)-2-methylphenyl] methanol or of its enantiomers as defined in the claims.

2. Summary of the related art

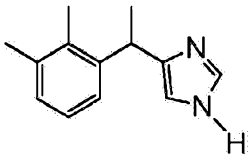
[0002] Three alpha-1 and three alpha-2 adrenergic receptors have been characterized by molecular and pharmacological methods. Activation of these alpha receptors evokes physiological responses with useful therapeutic applications.

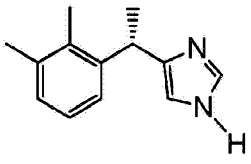
[0003] Compound, 4-[1-(2,3-dimethylphenyl)ethyl]-3*H*-imidazole, generically known as, medetomidine is an alpha 2 adrenergic agonist, for use in the sedation of animals. The hydrochloride salt of the (*S*) enantiomer of medetomidine, generically known as dexmedetomidine, (*S*) 4-[1-(2,3-dimethylphenyl)ethyl]-3*H*-imidazole, is also indicated for use as a sedative or analgesic in cats and dogs.

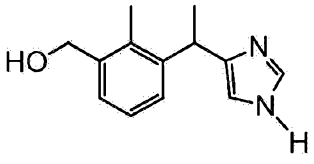
[0004] The metabolite of dexmedetomidine is (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol together with its racemic mixture, compound [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, are described in the literature in Journal of Chromatography, (1997), 762(1 + 2), 281-291 by Hui, Y.-H et al.

[0005] [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl]methanol is described in "Synthesis of detomidine and medetomidine metabolites: 1,2,3-trisubstituted arenes with 4'(5')-imidazolylmethyl groups" in Journal of Heterocyclic Chemistry (1993), 30(6), (1645-1651) by Stoilov et al.

[0006] Kavanagh, et al. describe [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl]methanol in "Synthesis of Possible Metabolites of Medetomidine {1-(2,3-dimethylphenyl)-1-[imidazol-4(5)-yl]ethane" in Journal of Chemical Research, Synopses (1993), (4), 152-3.







Medetomidine

4-(1-(2,3-dimethylphenyl) ethyl)-1*H*-imidazole

CAS 86347-14-0

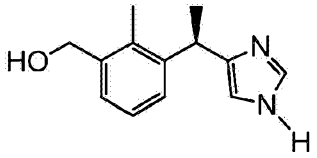
Dexmedetomidine

(*S*)-4-(1-(2,3-dimethylphenyl) ethyl)-1*H*-imidazole

CAS 189255-79-6

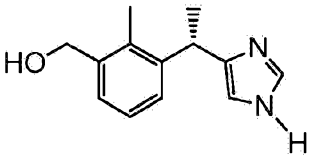
(3-(1-(1*H*-imidazol-4-yl)ethyl) -2-methylphenyl)methanol

CAS 128366-50-7



(*R*)-(3-(1-(1*H*-imidazol-4-yl)ethyl) -2-methylphenyl)methanol

CAS 1240244-32-9



(*S*)-(3-(1-(1*H*-imidazol-4-yl)ethyl) -2-methylphenyl)methanol

CAS 189255-79-6

[0007] [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl)methanol] is described by Salonen, et al. in "Biotransformation of Medetomidine in the Rat" in Xenobiotica (1990), 20(5), 471-80.

[0008] PCT Int. Appl. WO 2010093930 A1 discloses [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl]methanol and its (*S*) and (*R*) enantiomers.

SUMMARY OF THE INVENTION

[0009] Three alpha 1 and three alpha 2 adrenergic receptors have been characterized by molecular and pharmacological methods. Activation of these alpha 2 receptors evokes physiological responses and has useful therapeutic actions.

[0010] The present invention relates to a composition for use in a method of treating retinal diseases in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising ester pro-drugs of [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as defined in the claims. Upon hydrolytic and/or enzymatic cleavage of the ester functionality the parent compound, [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, is released to act as a selective modulator of the alpha 2 adrenergic receptors.

[0011] In another aspect, the present invention relates to a composition for use in a method of treating retinal diseases in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising ester pro-drugs of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as defined in the claims, or pharmaceutical compositions containing them. Upon hydrolytic and/or enzymatic cleavage of the ester functionality the parent compound, active metabolite, (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, is released to act as a selective modulator of the alpha 2 adrenergic receptors.

[0012] In another aspect the present invention relates to a composition for use in a method of treating retinal diseases in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising ester pro-drugs of (*R*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as defined in the claims, or pharmaceutical compositions containing them. Upon hydrolytic and/or enzymatic cleavage of the ester functionality the parent compound (*R*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, is released to act as a selective modulator of the alpha 2 adrenergic receptors.

[0013] The ester pro-drugs of [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol according to the present disclosure are useful for the treatment or prevention of a range of conditions and diseases in mammals, including humans, that are alleviated by alpha 2A, 2B, 2C activation, including but not limited to treating or preventing glaucoma, elevated intraocular pressure, ischemic neuropathies, optic neuropathy, pain, visceral pain, corneal pain, headache pain, migraine, cancer pain, back pain, irritable bowel syndrome pain, muscle pain and pain associated with diabetic neuropathy, the treatment of diabetic retinopathy, other retinal degenerative conditions, stroke, cognitive deficits, neuropsychiatric conditions, drug dependence and addiction, withdrawal of symptoms, obsessive-compulsive disorders, obesity, insulin resistance, stress-related conditions, diarrhea, diuresis, nasal congestion, spasticity, attention deficit disorder, psychoses, anxiety, depression, autoimmune disease, Crohn's disease, gastritis, Alzheimer's, and Parkinson's ALS other neurodegenerative diseases, dermatological conditions, skin erythema (redness) and inflammation, acne, age related macular degeneration, wet macular degeneration, dry macular degeneration, geographic atrophy, diabetic macular edema, tumors, wound healing, inflammation and retinal vein occlusion, enhancing vision in patients with vision loss from conditions including glaucoma, retinitis pigmentosa and neuritis secondary to multiple sclerosis, rosacea (dilation of the blood vessels just under the skin), sunburn, chronic sun damage, discreet erythemas, psoriasis, acne rosacea, menopause-associated hot flashes, hot flashes resulting from orchiectomyatopic dermatitis, photoaging, seborrheic dermatitis, allergic dermatitis, redness of the skin, telangiectasia (dilations of previously existing small blood vessels) of the face, rhinophyma (hypertrophy of the nose with follicular dilation), red bulbous nose, acne-like skin eruptions (may ooze or crust), burning or stinging sensation of the face, irritated and bloodshot and watery eyes, erythema of the skin, cutaneous hyperactivity with dilation of blood vessels of the skin, Lyell's syndrome, Stevens-Johnson syndrome, erythema multiforme minor, erythema multiforme major and other inflammatory skin diseases.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The present invention relates to a composition for use in a method of treating retinal diseases in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising ester pro-drugs of [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol and of (*R*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as

defined in the claims as alpha-2 agonists with therapeutic utility.

[0015] The term "subject", as used herein, refers to a human patient.

[0016] In a preferred embodiment the present invention relates to a composition for use in a method of treating retinal diseases in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising esters pro-drugs of (*S*)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as alpha-2 agonists with therapeutic utility as defined in the claims. Upon hydrolytic or enzymatic cleavage of the ester functionality the parent compound, active metabolite, (*S*)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, is released to act as a selective modulator of the alpha 2 adrenergic receptors.

[0017] In one aspect of the invention, there is provided a composition for use in a method for treating retinal diseases in a patient in need thereof which comprises, consists essentially of or consists of or consists of administering a therapeutically effective amount of a pharmaceutical composition comprising, consisting essentially of or consisting of a therapeutically effective amount of ester pro-drugs of [3-(1-(1 *H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as defined in the claims, or the tautomers thereof, or pharmaceutically acceptable salts thereof.

[0018] In another aspect of the invention, there is provided a composition for use in a method for treating retinal diseases in a patient in need thereof which comprises, consists essentially of or consists of or consists of administering a therapeutically effective amount of a pharmaceutical composition comprising, consisting essentially of or consisting of a therapeutically effective amount of ester pro-drugs (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as defined in the claims, or the tautomers thereof, or pharmaceutically acceptable salts thereof.

[0019] In another aspect of the invention, there is provided a composition for use in a method for treating retinal diseases in a patient in need thereof which comprises, consists essentially of or consists of or consists of administering a therapeutically effective amount of a pharmaceutical composition comprising, consisting essentially of or consisting of a therapeutically effective amount of ester pro-drugs of (*R*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as defined in the claims, or the tautomers thereof, or pharmaceutically acceptable salts thereof.

[0020] In another aspect of the invention, there is provided a composition for use in a method for treating retinal diseases including but not limited to: age related macular degeneration, wet macular degeneration, dry macular degeneration, geographic atrophy, diabetic retinopathy, diabetic macular edema and retinal vein occlusion. Our compound of interest is also useful for enhancing vision in patients with vision loss from conditions including ocular hypertension, glaucoma, retinitis pigmentosa, nyctalopia, and neuritis secondary to multiple sclerosis.

[0021] In another aspect of the invention, there is provided a composition for use in a method

for treating retinal diseases including but not limited to: age related macular degeneration, wet macular degeneration, dry macular degeneration, geographic atrophy, diabetic retinopathy, diabetic macular edema and retinal vein occlusion. Our compound of interest is also useful for enhancing vision in patients with vision loss from conditions including ocular hypertension, glaucoma, retinitis pigmentosa, nyctalopia, and neuritis secondary to multiple sclerosis, which comprises, consists essentially of or consists of or consists of administering a therapeutically effective amount of a pharmaceutical composition comprising, consisting essentially of or consisting of a therapeutically effective amount of ester pro-drugs of [3-(1-(1 *H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as defined in the claims, or the tautomers thereof, or pharmaceutically acceptable salts thereof.

[0022] In another aspect of the invention, there is provided a composition for use in a method for treating retinal diseases including but not limited to: age related macular degeneration, wet macular degeneration, dry macular degeneration, geographic atrophy, diabetic retinopathy, diabetic macular edema and retinal vein occlusion. Our compound of interest is also useful for enhancing vision in patients with vision loss from conditions including ocular hypertension, glaucoma, retinitis pigmentosa, nyctalopia, and neuritis secondary to multiple sclerosis, which comprises, consists essentially of or consists of or consists of administering a therapeutically effective amount of a pharmaceutical composition comprising, consisting essentially of or consisting of a therapeutically effective amount of ester pro-drugs of (*S*) [3-(1-(1 *H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as defined in the claims, or the tautomers thereof, or pharmaceutically acceptable salts thereof.

[0023] In another aspect of the invention, there is provided a composition for use in a method for treating retinal diseases including but not limited to: age related macular degeneration, wet macular degeneration, dry macular degeneration, geographic atrophy, diabetic retinopathy, diabetic macular edema and retinal vein occlusion. Our compound of interest is also useful for enhancing vision in patients with vision loss from conditions including ocular hypertension, glaucoma, retinitis pigmentosa, nyctalopia, and neuritis secondary to multiple sclerosis, which comprises, consists essentially of or consists of or consists of administering a therapeutically effective amount of a pharmaceutical composition comprising, consisting essentially of or consisting of a therapeutically effective amount of ester pro-drugs of (*R*) [3-(1-(1 *H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as defined in the claims, or the tautomers thereof, or pharmaceutically acceptable salts thereof.

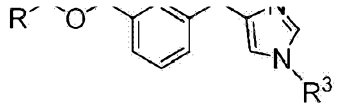
[0024] In another aspect of the invention, there is provided a composition for use in a method for treating retinal diseases wherein the pharmaceutical composition comprising, consisting essentially of or consisting of a therapeutically effective amount of ester pro-drugs of [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as defined in the claims, is selected from topical ocular application, direct injection, applications and formulations that may further enhance the long duration of actions such as a slow releasing pellet, suspension, gel, solution, cream, ointment, foams, emulsions, microemulsions, serums, aerosols, sprays, dispersions, microcapsules, vesicles, microparticles.

[0025] In another aspect of the invention, there is provided a composition for use in a method for treating retinal diseases wherein the pharmaceutical composition comprising, consisting essentially of or consisting of a therapeutically effective amount of ester pro-drugs of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as defined in the claims is selected from topical ocular application, direct injection, applications and formulations that may further enhance the long duration of actions such as a slow releasing pellet, suspension, gel, solution, cream, ointment, foams, emulsions, microemulsions, serums, aerosols, sprays, dispersions, microcapsules, vesicles, microparticles.

[0026] In another aspect of the invention, there is provided a composition for use in a method for treating retinal diseases wherein the pharmaceutical composition comprising, consisting essentially of or consisting of a therapeutically effective amount of ester pro-drugs of (*R*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol as defined in the claims is selected from topical skin application, direct injection, applications and formulations that may further enhance the long duration of actions such as a slow releasing pellet, suspension, gel, solution, lotion, cream, ointment, foams, emulsions, microemulsions, serums, aerosols, sprays, dispersions, microcapsules, vesicles, microparticles.

[0027] "Prodrugs" are frequently referred to by the term "metabolically cleavable derivatives" which refers to compound forms which are rapidly transformed in vivo to the parent compound according to the invention, for example, by hydrolysis in blood. Thus, prodrugs are compounds bearing groups which are removed by biotransformation prior to exhibiting their pharmacological action. Such groups include moieties which are readily cleaved in vivo from the compound bearing it, which compound after cleavage remains or becomes pharmacologically active. Such metabolically cleavable groups form a class well known to practitioners of the art. They include, but are not limited to such groups as alkanoyl (i.e. acetyl, propionyl, butyryl, and the like), unsubstituted and substituted carbocyclic aroyl (such as benzoyl, substituted benzoyl and 1- and 2-naphthoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethylsilyl), monoesters formed with dicarboxylic acids (such as succinyl), phosphate, sulfate, sulfonate, sulfonyl, sulfinyl and the like. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. (T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery System", Vol. 14 of the A.C.S. Symposium Series; "Bioreversible Carriers in Drug Design", ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987).

[0028] In one aspect, the disclosure therefore relates to a composition for use in a method of lowering intraocular pressure in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising a compound having Formula I, its individual enantiomers, its individual diastereoisomers, its individual hydrates, its individual solvates, its individual crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof,



Formula I

wherein

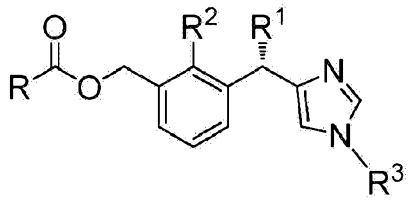
R^1 is H or C_{1-3} alkyl;

R^2 is H or C_{1-3} alkyl;

R^3 is H, C_{1-10} alkyl, heterocycle or aryl; and

R is C_{1-10} alkyl, heterocycle or aryl.

[0029] In a preferred aspect, the disclosure therefore relates to a composition for use in a method of lowering intraocular pressure in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising a compound having Formula II, its individual diastereoisomers, its individual hydrates, its individual solvates, its individual crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof,



Formula II

wherein

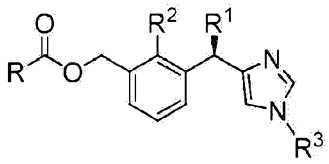
R^1 is H or C_{1-3} alkyl;

R^2 is H or C_{1-3} alkyl;

R^3 is H, C_{1-10} alkyl, heterocycle or aryl; and

R is C_{1-10} alkyl, heterocycle or aryl.

[0030] In another aspect, the disclosure therefore relates to a composition for use in a method of lowering intraocular pressure in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising a compound having Formula III, its individual diastereoisomers, its individual hydrates, its individual solvates, its individual crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof,



Formula III

wherein

R^1 is H or C_{1-3} alkyl;

R^2 is H or C_{1-3} alkyl;

R^3 is H, C_{1-10} alkyl, heterocycle or aryl; and

R is C_{1-10} alkyl, heterocycle or aryl.

[0031] The following paragraphs provide definitions of the various chemical moieties that make up the compounds of the invention and are intended to apply uniformly throughout the specification and claims unless expressly stated otherwise.

[0032] The term "alkyl" as used herein, is defined as including a saturated monovalent alkane moiety having straight or branched alkane moieties or combinations thereof and containing 1-10 carbon atoms, preferably 1-8 carbon atoms and more preferably 1-4 carbon atoms. Alkyl moieties can optionally be substituted by, but not limited to, amino groups, aryl groups, halogens. One methylene ($-CH_2-$) can be replaced by carbonyl, -NH-, carboxyl, amide, sulfur or by oxygen. Examples include, but are not limited to, methyl, ethyl, propyl, butyl, *sec*-butyl, pentyl, *iso*-pentyl, *neo*-pentyl, hexyl, *iso*-hexyl, 3-methyl-butyl, 2-amino-N-isobutyl acetamide, *iso*-butyl, *tert*-butyl, *iso*-propyl, ethylphenyl, methylphenyl, 2-amino-3-methyl-butanamide-N-2-methyl-1-propyl, 1-amino-2-methyl-prop-1-yl.

[0033] The term "heterocycle" as used herein is defined as an aromatic or non aromatic 5 to 10 membered monocyclic or bicyclic ring containing at least one heteroatom selected from O or N or S or combinations thereof, interrupting the carbocyclic ring structure. Heterocycles can optionally be substituted by, but not limited to, C_{1-6} alkyl, amino, halogen, $-O(C_{1-6}$ alkyl), $-OC(O)(C_{1-6}$ alkyl), $-C(O)O(C_{1-6}$ alkyl), $-NHC(O)(C_{1-6}$ alkyl), $-C(O)NH(C_{1-6}$ alkyl), $-S(C_{1-6}$ alkyl) groups. Examples include, but are not limited to, furyl, pyrryl, pyridyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, pyrazinyl, benzofuranyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl, oxazolyl, thiazolyl, isothiazolyl, 1,2,5-thiadiazolyl, 1,2,4-thiadiazolyl, isooxazolyl, quinazolinyl, pyridazinyl, cinnolinyl, phthalazinyl, quinoxalinyl, xanthinyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, pyrrolidinyl, piperidinyl and piperazinyl.

[0034] The term "aryl" as used herein, is defined as including an organic moiety derived from an aromatic hydrocarbon consisting of a monocyclic or bicyclic ring containing 6-10 carbon atoms by removal of one hydrogen atom, such as phenyl or naphthyl. Aryl groups can optionally be substituted by, but not limited to, C_{1-6} alkyl, amino, halogen, -O(C_{1-6} alkyl), -OC(O)(C_{1-6} alkyl), -C(O)O(C_{1-6} alkyl), -NHC(O)(C_{1-6} alkyl), - C(O)NH(C_{1-6} alkyl), -S(C_{1-6} alkyl) groups. Examples include, but are not limited to, phenyl, naphthyl.

[0035] The term "H" as used herein refers to a hydrogen atom.

[0036] The term "O" as used herein refers to an oxygen atom.

[0037] The term "S" as used herein refers to a sulfur atom.

[0038] The term "N" as used herein refers to a nitrogen atom.

[0039] The term "amino" as used herein refers to a group of formula -NH_2.

[0040] The term "amide" as used herein refers to a group of formula -C(O)NH- or -NHC(O)-.

[0041] The term "halogen", as used herein refers to an atom of chlorine, bromine, iodine or fluorine.

[0042] The term "carbonyl" as used herein refers to a group of formula -C=O.

[0043] The term "carboxyl", as used herein refers to a group of formula -C(O)O- or -OC(O)-.

[0044] R^1 is H or C_{1-3} alkyl. Preferred R^1 is C_{1-3} alkyl. Most preferred R^1 is methyl.

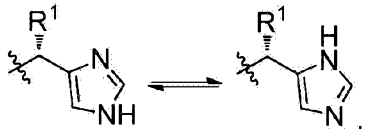
[0045] R^2 is H or C_{1-3} alkyl. Preferred R^2 is C_{1-3} alkyl. Most preferred R^2 is methyl.

[0046] R^3 is H, C_{1-10} alkyl, heterocycle or aryl. Preferred R^3 is H, phenyl or C_{1-10} alkyl. Most preferred R^3 is H.

[0047] R is C_{1-10} alkyl, heterocycle or aryl. Preferred R is methyl, *iso*-butyl, *tert*-butyl, *iso*-propyl, ethylphenyl, phenyl, 2-amino-1-phenylethyl, 2-(2-amino-3-methyl-butyrylamino)-2-methyl-prop-1-yl, 1-amino-2-methyl-prop-1-yl, 2-(2-amino-acetylamino)-2-methyl- prop-1-yl. Most preferred R groups are *tert*-butyl, iso-propyl.

[0048] As used herein, "tautomer" refers to the migration of protons between adjacent single and double bonds. The tautomerization process is reversible. Compounds described herein can undergo any possible tautomerization that is within the physical characteristics of the compound. The following is a tautomerization example that can occur in compounds described

herein:



[0049] Compounds for use according to the present invention are:

iso-Butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2,2-Dimethyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

Acetic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

Benzoic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

3-Methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

3-Phenyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-Amino-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-(2-Amino-3-methyl-butyrylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-(2-Amino-acetylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-Amino-3-phenyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester.

[0050] Intermediates used in preparation of the compounds for use in the present invention are:

iso-Butyric acid 3-[(*S*)-1-(1-*iso*-butyryl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2,2-Dimethyl-propionic acid 3-{(*S*)-1-[1-(2,2-dimethyl-propionyl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester;

Acetic acid 3-[(*S*)-1-(1-acetyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

Benzoic acid 3-[(*S*)-1-(1-benzoyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

3-Methyl-butyric acid 2-methyl-3-{(*S*)-1-[1-(3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-benzyl ester;

Phenyl-propionic acid 2-methyl-3-{(*S*)-1-[1-(3-phenyl-propionyl)-1*H*-imidazol-4-yl]-ethyl}-benzyl ester;

2-*tert*-Butoxycarbonylamino-3-methyl-butyric acid 3-{(*S*)-1-[1-(2-*tert*-butoxycarbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester;

2-*tert*-Butoxycarbonylamino-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-(2-*tert*-Butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-butyric acid 3-{(*S*)-1-[1-(2-*tert*-butoxycarbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester;

2-(2-*tert*-Butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-(2-*tert*-Butoxycarbonylamino-acetylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester;

2-*tert*-Butoxycarbonylamino-3-phenyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester.

[0051] Some compounds of Formula I , Formula II and Formula III and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in an *(R)* or (*S*) configuration, said (*R*) and (*S*) notation is used in correspondence with the rules described in Pure Appli. Chem. (1976), 45, 11-13.

[0052] Compounds for use according to the present invention may exist in different polymorphic forms. Although not explicitly indicated in the above formula, such forms are intended to be included within the scope of the present invention.

[0053] Compounds of Formula I, Formula II or Formula III and their salts can be in the form of a solvate for use in the invention, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

[0054] The term "pharmaceutically acceptable salts" refers to salts or complexes that retain the desired biological activity of the above identified compounds and exhibit minimal or no undesired toxicological effects. The "pharmaceutically acceptable salts" for use in the invention include therapeutically active, non-toxic base or acid salt forms, which the compounds of Formula I, Formula II or Formula III are able to form.
The acid addition salt form of a compound of Formula I, Formula II or Formula III that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example but not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; or an organic acid such as for example but not limited to, as citric acid, acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic, and polygalacturonic acid as well as base addition salts such as those formed with alkali- and alkaline earth metals such as sodium,

potassium and calcium and the like (Handbook of Pharmaceutical Salts, P.Heinrich Stahl & Camille G. Wermuth (Eds), Verlag Helvetica Chimica Acta-Zürich, 2002, 329-345).

[0055] The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include, but not limiting to the quaternary ammonium salt of the formula $-NY^+Z^-$, wherein Y is hydrogen, alkyl, or benzyl, and Z is a counterion, including but not limited to, chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as fumarate, benzoate, succinate, acetate, glycolate, maleate, malate, fumarate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate).

[0056] In another embodiment of the invention, there are provided pharmaceutical compositions including at least one compound for use in the invention in a pharmaceutically acceptable carrier thereof. The phrase "pharmaceutically acceptable" means the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0057] Pharmaceutical compositions for use in the present invention can be in the form of a solid, a solution, an emulsion, a dispersion, a patch, a micelle, a liposome, and the like, wherein the resulting composition contains one or more compounds for use in the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for enteral or parenteral applications. Compounds for use in the invention may be combined, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include but are not limited to, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. Compounds for use in the invention are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or disease condition.

[0058] Pharmaceutical compositions containing compounds for use in the invention may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, or saccharin, flavoring agents such as peppermint, oil of wintergreen or cherry, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets containing compounds for use in the invention in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating

agents such as corn starch, potato starch or alginic acid; (3) binding agents such as gum tragacanth, corn starch, gelatin or acacia, and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the compounds for use in the invention are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the compounds for use in the invention are mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[0059] The pharmaceutical compositions may be in the form of a sterile injectable suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides, fatty acids (including oleic acid), naturally occurring vegetable oils like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or the like. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

[0060] The present disclosure concerns also the use of a compound of Formula I, Formula II or Formula III, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the therapeutic application. The present disclosure concerns also the method for manufacturing a medicament intended for therapeutic application wherein a compound having general Formula I, Formula II or Formula III, or a pharmaceutically active derivative or salt thereof is used.

[0061] Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration and dosage employed for each subject is left to the discretion of the practitioner. The patient will be administered the compound orally in any acceptable form, such as a tablet, liquid, capsule, powder and the like, or other routes may be desirable or necessary, particularly if the patient suffers from nausea. Such other routes may include, without exception, transdermal, parenteral, subcutaneous, intranasal, via an implant stent, intrathecal, intravitreal, topical to the eye, back to the eye, intramuscular, intravenous, and intrarectal modes of delivery. The actual amount of the compound to be administered in any given case will be determined by a physician taking into account the relevant circumstances, such as the severity of the condition, the age and weight of the patient, the patient's general physical condition, the cause of the condition, and the route of administration. Additionally, the formulations may be designed to delay release of the active compound over a given period of time, or to carefully control the amount of drug released at a given time during the course of therapy.

[0062] Ester pro-drugs of [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol or of (*R*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol and their pharmaceutically-acceptable salts may be administered through different routes, including but not limited to topical eye drops, direct injection, application at the back of the eye or formulations that may further enhance the long duration of actions such as a slow releasing pellet, suspension, gel, or sustained delivery devices such as any suitable drug delivery system (DDS) known in the art. While topical administration is preferred, this compound may also be used in an intraocular implant as described in U.S. U.S. Patent 7,931,909. Such biocompatible intraocular implants include ester pro-drugs of [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol or of (*R*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol and a polymer associated with ester pro-drugs of [3-(1-(*1H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol or of (*R*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol to facilitate release thereof into an eye for an extended period of time.

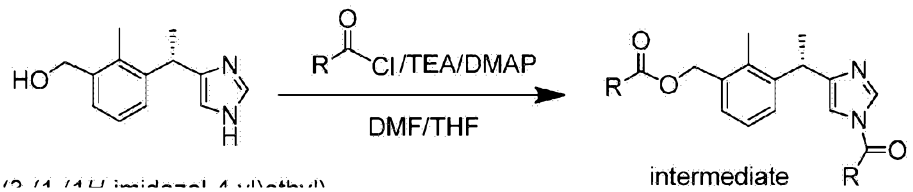
[0063] Ophthalmic formulations of drug products are well known in the art and described in, for example, U.S. Patent Application Publication No. 20050059583; No. 20050277584; U.S. Patent No. 7,297,679; and No. 20070015691; and U.S. Patent Nos. 5,474,979 and 6,582,718. The ester pro-drugs of [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol or of (*R*) [3-(1-(1H-imidazol-4-yl)ethyl)-2-methylphenyl] methanol may be formulated with efficacy enhancing components as disclosed in U.S. Patent Number 7,491,383 B2.

[0064] With respect to the present invention reference to a compound or compounds, is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to specifically.

[0065] The present disclosure also concerns a process for preparing the compounds having general Formula I, Formula II or Formula III. The synthetic scheme set forth below, illustrates how compounds for use in the invention can be made. Those skilled in the art will be able to routinely modify and/or adapt the following scheme to synthesize any compounds for use in the invention covered by Formula I, Formula II or Formula III.

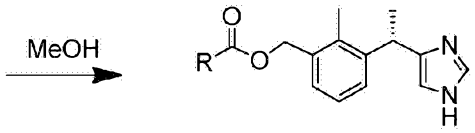
General scheme for synthesizing ester prodrugs of (*S*)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl]methanol

[0066]



(*S*)-(3-(1-(1*H*-imidazol-4-yl)ethyl) intermediate

(S)-(3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl)methanol



R^3 is H

In a first step (*S*)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol (CAS 189255-79-6) can react with the desired acyl chloride, in the presence of *N,N*-dimethyl formamide (DMF), tetrahydrofuran (THF), triethylamine (TEA) and 4-dimethyl aminopyridine (DMAP). After a typical work-up by extraction, the residue can be purified by medium pressure liquid chromatography (MPLC) (0% to 40% ethyl acetate in hexanes) to yield the intermediate compound as a solid.

[0067] In a second step, the intermediate obtained in the first reaction, can react with methanol (MeOH). The residue can be purified by MPLC (50% ethyl acetate in hexanes then 5% 7N ammonia/ methanol /dichloromethane) to yield the desired compound as a solid.

[0068] As used herein, the use of the singular includes the plural unless specifically stated otherwise.

[0069] The present invention includes all pharmaceutically acceptable isotopically enriched compounds. Any compound for use in the invention may contain one or more isotopic atoms enriched or different than the natural ratio such as deuterium ^{2}H (or D) in place of protium ^{1}H (or H) or use of ^{13}C enriched material in place of ^{12}C and the like. Similar substitutions can be employed for N, O and S. The use of isotopes may assist in analytical as well as therapeutic aspects of the invention. For example, use of deuterium may increase the *in vivo* half-life by altering the metabolism (rate) of the compounds for use in the invention. These compounds can be prepared in accord with the preparations described by use of isotopically enriched reagents.

[0070] The IUPAC names of the compounds mentioned in the examples were generated with ACD version 8.

[0071] Unless specified otherwise in the examples, characterization of the compounds is performed according to the following methods:
NMR spectra are recorded on 300 MHz Varian and acquired at room temperature. Chemical shifts are given in ppm referenced either to internal TMS or to the residual solvent signal.

[0072] All the reagents, solvents, catalysts for which the synthesis is not described are purchased from chemical vendors such as Sigma Aldrich, Fluka, Lancaster, however some known reaction intermediates, for which the CAS registry number is mentioned, were prepared in-house following known procedures.
Usually the compounds for use in the invention were purified by flash column chromatography.

[0073] The following abbreviations are used in the examples:

DCM
: dichloromethane

MeOH
: methanol

CD_3OD
: deuterated methanol

NH_3
: ammonia

Na_2SO_4
: sodium sulfate

DMF
: N,N-dimethylformamide

$MgSO_4$
: magnesium sulfate

EtOAc
: ethylacetate

i-PrOH
: *iso*-propanol

$CDCl_3$
: deuterated chloroform

MPLC
: medium pressure liquid chromatography

DMF
: dimethylformamide

TEA
: triethylamine

THF
: tetrahydrofuran

DMAP
: 4-dimethylaminopyridine

RT
: room temperature

Boc-L-Valine
: N-(*tert*-Butoxycarbonyl)-L-valine

Boc-Glycine
: N-(*tert*-Butoxycarbonyl)glycine

Boc-L-Phenylalanine
: N-(*tert*-Butoxycarbonyl)-L-phenylalanine

HCl
: hydrochloric acid

H_2O
: water

EDCI

1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

$NaHCO_3$

sodium bicarbonate

Example 1

Intermediate 1

***iso*-Butyric acid 3-[(*S*)-1-(1-isobutyry)-1*H*-imidazol-4-yl)-ethyl] -2-methyl-benzyl ester**

[0074] To a solution of (*S*)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol (1.34g, 6.2mmol) in DMF (8ml) and THF (50ml), were added TEA (3.5ml, 24.8mmol), DMAP (780mg, 6.2mmol) and *iso*-butyryl chloride (2.18g, 20.5mmol). The resulting mixture was stirred at RT for 16 h, quenched with H_2O and extracted with ethyl acetate. The combined organic layers were washed with brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPLC (0% to 40% ethyl acetate in hexanes) to yield **Intermediate 1** as solid.

[0075] ^{1}H-NMR (CD_3OD, δ ppm): 1.15 (d, J=7.03Hz, 6H), 1.26 (d, 6H, J=6.74Hz), 1.56 (d, J=7.03Hz, 3H), 2.34 (s, 3H), 2.58 (hept, J=7.03Hz, 1H), 3.34(hept, J=7.74Hz, 1H), 4.42(q, J=7.03Hz, 1H), 5.15(s, 2H), 7.07-7.10 (m, 2H), 7.12-7.15 (m, 1H), 7.31 (s, 1H), 8.35 (s, 1H).

[0076] Intermediates 2-6 were prepared in a similar manner to the method described in **Example 1** starting with (*S*)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol. The acyl chloride used in each case and the results are tabulated below in T**able 1.**

T**able 1**

Intermediate number	IUPAC name	Acyl chloride	^{1} NMR (Solvent; δ ppm)
2	**2,2-Dimethyl-propionic acid 3-{(*S*)-1-[1-(2,2-dimethyl-propionyl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester**	Pivaloyl chloride	(CD_3OD): 1.19 (s, 9H), 1.42 (s, 9H), 1.56 (d, J=7.03Hz, 3H), 2.34 (s, 3H), 4.42(q, J=7.03Hz, 1H), 5.15(s, 2H), 7.07-7.10 (m, 2H), 7.12-7.15 (m, 1H), 7.33 (s, 1H), 8.40 (s, 1H).

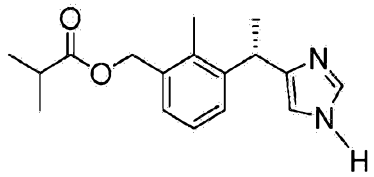
Intermediate number	IUPAC name	Acyl chloride	^{1} NMR (Solvent; δ ppm)
3	**Acetic acid 3-[(*S*)-1-(1-acetyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester**	Acetyl chloride	(CD_3OD): 1.55 (d, J=7.03Hz, 3H), 2.05 (s, 3H), 2.33 (s, 3H), 2.58 (s, 3H), 4.39(q, J=7.03Hz, 1H), 5.15(s, 2H), 7.07-7.10 (m, 2H), 7.12-7.15 (m, 1H), 7.30 (s, 1H), 8.29 (s, 1H).
4	**Benzoic acid 3-[(*S*)-1-(1-benzoyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester:**	Benzoyl chloride	(CD_3OD): 1.58 (d, J=7.03Hz, 3H), 2.43 (s, 3H), 4.46(q, J=7.03Hz, 1H), 5.41 (s, 2H), 7.11-7.18 (m, 2H), 7.27-7.35 (m, 2H), 7.42-7.50 (m, 2H), 7.50-7.63 (m, 3H), 7.65-7.71 (m, 1H), 7.79 (d, J=7.33Hz, 2H), 8.00 (d, J=7.33Hz, 2H), 8/09 (s, 1H).
5	**3-Methyl-butyric acid 2-methyl-3-{(*S*)-1-[1-(3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-benzyl ester**	Methylbutanoyl chloride	(CD_3OD): 0.91 (d, J=6.44Hz, 6H), 1.01 (d, J=6.44Hz, 6H), 1.54 (d, J=7.03Hz, 3H), 2.05 (hept, J=6.44Hz, 1H), 2.15-2.25 (m, 3H), 2.33 (s, 3H), 2.81 (d, J=7.03Hz, 3H), 4.42(q, J=7.03Hz, 1H), 5.14(s, 2H), 7.07-7.19 (m, 3H), 7.28 (s, 1H), 8.32 (s, 1H).
6	**3-Phenyl-propionic acid 2-methyl-3-{(*S*)-1-[1-(3-phenyl-propionyl)-1*H*-imidazol-4-yl]-ethyl}-benzyl ester**	Phenylpropanoyl chloride	(CD_3OD): 1.52 (d, J=7.03Hz, 3H), 2.24 (s, 3H), 2.64 (t, J=7.61 Hz, 2H), 2.90 (t, J=7.61 Hz, 2H), 3.04 (t, J=7.61 Hz, 2H),3.24 (t, J=7.61 Hz, 2H), 4.34 (q, J=7.03Hz, 1H), 5.13 (s, 2H), 7.08-7.248 (m, 14H), 8.25 (s, 1H).

Example 2

Compound 1

***iso*-Butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester**

[0077]

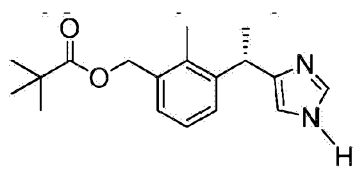
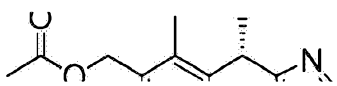


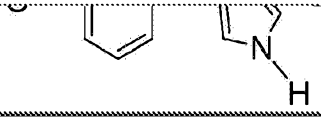
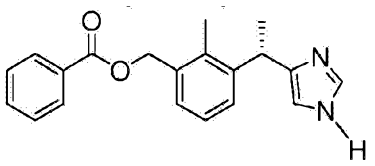
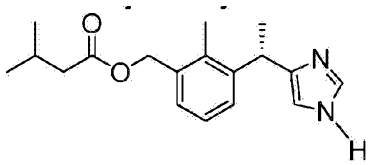
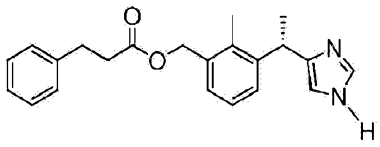
[0078] Intermediate 1 was dissolved in MeOH (50ml) and the mixture was stirred at RT for 24 h and then concentrated under reduced pressure. The residue was purified by MPLC (50% ethyl acetate in hexanes then 5% 7N NH_3/ MeOH /DCM) to yield **Compound 1** as a solid.

[0079] ^{1}H-NMR (CD_3OD; δ ppm): 1.15 (d, J=7.03Hz, 6H), 1.54 (d, J=7.03Hz, 3H), 2.33 (s, 3H), 2.56 (hept, J=7.03Hz, 1H), 4.42(q, J=7.03Hz, 1H), 5.15(s, 2H), 6.70 (s, 1H), 7.07-7.10 (m, 2H), 7.12-7.15 (m, 1H), 7.55 (s, 1H).

[0080] Compounds 2-6 for use in the invention were prepared according to the procedure described in **Example 2,** by reacting the corresponding intermediate with methanol. The results are tabulated below in **Table 2.**

Table 2

Comp. No.	IUPAC name	Inter. No.	^{1}NMR (Solvent, δ ppm)
2	**2,2-Dimethyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester** 	2	(CD_3OD): 1.19 (s, 9H), 1.54 (d, J=7.03Hz, 3H), 2.33 (s, 3H), 4.42 (q, J=7.03Hz, 1H), 5.13 (s, 2H), 6.70 (s, 1H), 7.07-7.10 (m, 2H), 7.12-7.15 (m, 1H), 7.55 (s, 1H).
3	**Acetic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl Ester**	3	(CD_3OD): 1.54 (d, J=7.03Hz, 3H), 2.04 (s, 3H), 2.33 (s, 3H), 4.42 (q, J=7.03Hz, 1H), 5.13 (s, 2H), 6.70 (s, 1H), 7.07-7.10 (m, 2H), 7.12-7.15 (m, 1H), 7.55 (s, 1H).
			

Comp. No.	IUPAC name	Inter. No.	^{1}NMR (Solvent, δ ppm)
			
4	**Benzoic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester** 	4	(CD_3OD): 1.54 (d, J=7.03Hz, 3H), 2.31 (s, 3H), 4.42(q, J=7.03Hz, 1H), 5.13 (s, 2H), 6.70 (s, 1H), 7.07-7.15 (m, 2H), 7.25-7.28 (m, 1H), 7.54-7.47 (m, 2H), 7.55-7.60 (m, 2H), 8.0 (d, J=7.33Hz, 2H).
5	**3-Methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl Ester** 	5	(CD_3OD): 0.93 (d, J=7.03Hz, 6H), 1.54 (d, J=7.03Hz, 3H), 2.07 (hept, J=7.03Hz, 1H), 2.21 (d, J=7.03Hz, 2H), 2.33 (s, 3H), 4.42(q, J=7.03Hz, 1H), 5.15(s, 2H), 6.70 (s, 1H), 7.07-7.10 (m, 2H), 7.12-7.15 (m, 1H), 7.55 (s, 1H).
6	**3-Phenyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl Ester** 	6	(CD_3OD): 1.54 (d, J=7.03Hz, 3H), 2.23 (s, 3H), 2.65 (t, J=7.61 Hz, 2H), 2.91 (t, J=7.61 Hz, 2H), 4.40 (q, J=7.03Hz, 1H), 5.13 (s, 2H), 6.70 (s, 1H), 7.08-7.24 (m, 8H), 7.55 (s, 1H).

Example 3

Intermediate 7

2-*tert*-Butoxycarbonylamino-3-methyl-butyric acid 3-{(*S*)-1-[1-(2-*tert*-butoxycarbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester

[0081] To a solution of (*S*)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol (216mg, 1.0mmol) in DMF (2ml) and THF (12ml) were added EDCI (671mg, 3.5mmol), DMAP (427mg, 3.5mmol) and Boc-L-Valine (651mg, 3.0mmol). The mixture was stirred at RT for 16 h,

quenched with H_2O and extracted with ethyl acetate. The combined organic layers were washed with H_2O, brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by a column chromatography (30% ethyl acetate in hexanes) to yield **Intermediate 7** as a white solid.

[0082] ^{1}H-NMR (CD_3OD; δ ppm): 0.85-1.01 (m, 12H), 1.20-1.48 (m, 18H), 1.56 (d, J=7.03Hz, 3H), 2.01-2.20(m, 2H), 2.35 (s, 3H), 4.03(m, 1H), 4.42 (q, J=7.03Hz, 1H), 4.60-4.65 (m, 1H), 5.15-5.29 (m, 2H), 7.10-7.20 (m, 2H), 7.20-7.25 (m, 1H), 7.33 (s, 1H), 8.44 (s, 1H).

Example 4

Intermediate 8

2-*tert*-Butoxycarbonylamino-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0083] The title compound was prepared from **Intermediate 7** (600mg, 0.98mmol) in 30ml of MeOH according to the procedure described in **Example 2.**

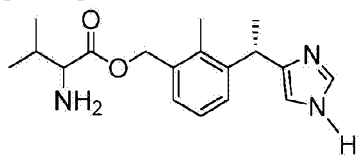
[0084] ^{1}H-NMR (CD_3OD; δ ppm): 0.85-0.95 (m, 6H), 1.42 (m, 9H), 1.54 (d, J=7.03Hz, 3H), 2.05 (m, 1H), 2.33 (s, 3H), 4.00 (d, J=6.15Hz, 1H), 4.40 (q, J=7.03Hz, 1H), 5.15-5.28 (m, 2H), 6.67 (s, 1H), 7.10-7.20 (m, 2H), 7.20-7.25 (m, 1H), 7.55 (s, 1H).

Example 5

Compound 7

2-Amino-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0085]



[0086] To **Intermediate 8** (390mg, 0.94mmol) was added 4N HCl in dioxane (8ml). The resulting solution was stirred at RT for 4 hrs, then quenched with H_2O, neutralized with aqueous saturated $NaHCO_3$ and extracted with 25% isopropyl alcohol in chloroform. The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by a column chromatography (5% 7N NH_3/MeOH in DCM) to yield **Compound 7** as a white solid.

[0087] ^{1}H-NMR (CD_3OD; δ ppm): 0.85 (d, J=6.74Hz, 3H), 0.91 (d, J=6.74Hz, 3H), 1.54 (d, J=7.03Hz, 3H), 1.96 (hept, J=6.74Hz, 1H), 2.33 (s, 3H), 3.28 (d, J=6.74Hz, 2H), 4.42 (q, J=7.03Hz, 1H), 5.20-5.25 (m, 2H), 6.67 (s, 1H), 7.10-7.12 (m, 2H), 7.13-7.20 (m, 1H), 7.55 (s, 1H).

Example 6

Intermediate 9

2-(2-*tert*-Butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-butyric acid 3-{(*S*)-1-[1-(2-*tert*-butoxycarbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzyl ester

[0088] The title compound was prepared from **Compound 7** (490mg, 1.55mmol), Boc-L-Valine (1.01g, 4.67mmol), EDCI (1.04g, 5.42mmol) and DMAP (671mg, 5.5mmol) according to the procedure described in **Example 3.**

[0089] ^{1}H-NMR (CD_3OD; δ ppm): 0.85-0.92 (m, 12H), 1.43 (s, 9H), 1.55 (d, J=7.03Hz, 3H), 1.97 (m, 1H), 2.14 (hept, J=6.60Hz, 1H), 2.35 (s, 3H), 3.88 (d, J=7.30Hz,, 1H), 4.35 (d, J=6.90Hz, 1H), 4.42(, d, J=7.03Hz, 1H), 5.18-5.25 (m, 2H), 6.67 (s, 1H), 7.10-7.15 (m, 2H),7/17-7.20 (m, 1H), 7.55 (s, 1H).

Example 7

Intermediate 10

2-(2-*tert*-Butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0090] The title compound was prepared from **Intermediate 9** (750mg, 1.05mmol) in 30ml of MeOH according to the procedure described in **Example 2.**

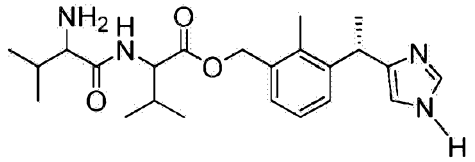
[0091] ^{1}H-NMR (CD_3OD; δ ppm): 0.89 (d,d , J=7.03Hz, 6H), 1.44 (s, 9H), 1.54 (d, J=7.33Hz, 3H), 2.14 (hept, J=6.74Hz, 1H), 2.33 (s, 3H), 3.74 (s, 2H), 4.35-4.55 (m, 2H), 5.20 (s, 2H), 6.67 (s, 1H), 7.10-7.17 (m, 2H), 7.19-7.23 (m, 1H), 7.56 (s, 1H).

Example 8

Compound 8

2-(2-Amino-3-methyl-butyrylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0092]



[0093] The title compound was prepared from **Intermediate 10** (450mg, 0.87mmol) in 8ml of 4N HCl/Dioxane according to the procedure described in **Example 5.**

[0094] ^{1}H-NMR (CD_3OD; δ ppm): 0.85 (d, J=7.03Hz, 3H), 0.91 (d, J=6.74Hz, 3H), 0.92 (d, J=7.3Hz. 3H), 1.14 (d, J=6.2Hz, 3H), 1.54 (d, J=7.03Hz, 3H), 1.94 (hept, J=5.2Hz, 1H), 2.14 (hept, J=6.2Hz, 1H), 2.33 (s, 3H), 3.18 (d, J=5.2Hz, 1H), 4.34 (d, J=6.2Hz, 1H), 4.42(q, J=7.03Hz, 1H), 5.21-5.26 (m, 2H), 6.67 (s, 1H), 7.10-7.15 (m, 2H), 7.18-7.20 (m, 1H), 7.55 (s, 1H).

Example 9

Intermediate 11

2-(2-*tert*-Butoxycarbonylamino-acetylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0095] The title compound was prepared from **Compound 8** (405mg, 1.28mmol), Boc-Glycine(675mg, 3.86mmol), EDCI(859mg, 4.48mmol) and DMAP(547mg, 4.48mmol) according to the procedure described in **Example 3.** The title compound was purified by column chromatography using 5% 7N NH_3/MeOH in DCM .

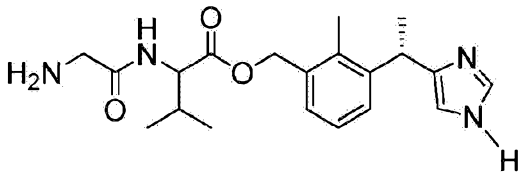
[0096] ^{1}H-NMR (CD_3OD; δ ppm): 0.89 (d, J=6.74Hz, 3H), 0.91 (d, J=6.74Hz, 3H), 1.55 (d, J=7.30Hz, 3H), 2.14 (hept, J=6.74Hz, 1H), 2.33 (s, 3H), 4.37 (d, J=5.90Hz, 1H), 4.42(q, J=7.03Hz, 1H), 5.20-5.25 (m, 2H), 6.67 (s, 1H), 7.10-7.12 (m, 2H), 7.13-7.20 (m, 1H), 7.55 (s, 1H).

Example 10

Compound 9

2-(2-Amino-acetylamino)-3-methyl-butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0097]



[0098] The title compound was prepared from **Intermediate 11** (320mg, 0.68mmol) with 10ml of 4N HCl/Dioxane according the procedure described in **Example 5.**

[0099] ^{1}H-NMR (CD_3OD; δ ppm): 0.89 (d, J=6.74Hz, 3H), 0.91 (d, J=6.74Hz, 3H), 2.14 (hept, J=6.74Hz, 1H), 2.33 (s, 3H), 4.37 (d, J=5.90Hz, 1H), 4.42(q, J=7.03Hz, 1H), 5.20-5.25 (m, 2H), 6.67 (s, 1H), 7.10-7.12 (m, 2H), 7.13-7.20 (m, 1H), 7.55 (s, 1H).

Example 11

Intermediate 12

2-*tert*-Butoxycarbonylamino-3-phenyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0100] The title compound was prepared from (*S*)-[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol (216mg, 1.0mmol), Boc-L-Phenylalanine(795mg, 3.0mmol), EDCI(671mg, 3.5mmol) and DMAP(427mg, 3.5mmol) according to the procedure described in **Example 3. Intermediate 12** was purified by a column chromatography using 35-100% ethyl acetate in hexane.

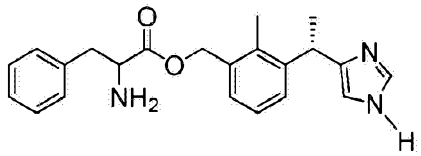
[0101] ^{1}H-NMR (CD_3OD; δ ppm): 1.36 (s, 9H), 1.55 (d, J=7.03Hz, 3H), 2.28 (s, 3H), 2.85-2.95 (m, 1H), 3.05-3.11(m, 1H), 4.38(m, 1H), 4.40(q, J=7.03Hz, 1H), 5.17(s, 2H), 6.69 (s, 1H), 7.08-7.24 (m, 8H), 7.55 (s, 1H).

Example 12

Compound 10

2-Amino-3-phenyl-propionic acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester

[0102]



[0103] The title compound was prepared from **Intermediate 12** (240mg, 0.52mmol) with 8ml of 4N HCl/Dioxane according to the procedure described in **Example 5.**

[0104] ^{1}H-NMR (CD_3OD; δ ppm): 1.54 (d, J=7.03Hz, 3H), 2.26 (s, 3H), 2.90-3.00 (m, 2H), 3.73 (t, J=6.40Hz, 1H), 4.40(q, J=7.03Hz, 1H), 5.13-5.18(m, 2H), 6.68 (s, 1H), 7.08-7.12 (m, 5H), 7.13-7.22 (m, 3H), 7.55 (s, 1H).

[0105] The following assay was used to demonstrate the potency and selectivity of the compounds for use in the invention.

Example 13

Visual enhancement model

[0106] Sixteen pigmented (Dutch-Belted) rabbits weighing 2-3 kg are used to evaluate the neuroenhancement effect of pro-drug *iso*-Butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester. Rabbits are dosed with pro-drug *iso*-Butyric acid 3-[(S)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester through intravenous route. Spatial sweep visual evoked potential (sVEP) acuity is assessed with PowerDiva software version 1.8. Recordings were made bilaterally in conscious animals. The results demonstrate that pro-drug *iso*-Butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester enhances visual acuity at 10-30 minutes post-dose in normal DB rabbits.

Example 14

The nerve crush model

[0107] This example describes the neuroprotective effect of pro-drug *iso*-Butyric acid 3-[(S)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester level in the rat nerve crush model. Sprague Dawley rats weighing 300-350 g were anesthetized with a mixture of ketamine (50mg/kg) and xylazine (0.5 mg/kg). Lateral canthotomy was performed in the right eye and an incision was made in the superior conjunctiva adjacent to the rectus muscle. This was followed by a blunt dissection until optic nerve was exposed. A partial compression was applied to the optic nerve for 30 seconds, 2 to 3 mm distal from the globe, using calibrated cross-acting forceps. Care was taken not to interfere with retinal blood supply. Pro-drug *iso*-Butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester was administered at 0.03, 0.1, 0.3, 1 mg/kg SC two hours before nerve injury, the vehicle PBS was administered SC as a negative control whereas brimonidine 0.1mg/kg was given by IP injection as a positive control. Control animals receive phosphate-buffered saline (PBS) vehicle. The experiment was terminated 12-15 days later.

Example 15

The chronic ocular hypertension model

[0108] Intraocular Pressure (IOP) was elevated in male Witar rats weighing 350-450 g using laser photocoagulation with blue-green argon laser (Coherent, Palo Alto, CA). Rats were anesthetized with a mixture of ketamine (15 mg/kg), acepromazine (1.5 mg/kg), and xylazine (0.3 mg/kg). Laser treatment was done in two parts (1-week interval) on limbal and episcleral

veins. The amount of energy used was 1 W for 0.2 seconds, delivering a total of 150 spots (50-100 (μM). Intraocular pressure was measured using tonometer (TONO-PEN: mentor, Norwell, MA). Rats were sedated with 3.0 mg/kg IM acepromazine during IOP measurements. Proparacaine 0.5% was applied topically on the eyes to anesthetize the cornea. Initial IOP measurements were done before laser treatment to determine baseline IOP and subsequent measurements were done once a week.

[0109] Pro-drug *iso*-Butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester is administered constantly using an osmotic pump (Alzet Osmotic Pumps, Durect Corp., Cupertino, CA) which was inserted subcutaneously on the back at 0.03, 0.1, 0.3, 1 mg/kg/day SC two hours before the first laser treatment (preventive mode) or following the second laser treatment (therapeutic mode). The vehicle PBS was administered by SC osmotic pump as a negative control whereas brimonidine 0.1mg/kg was given by IP injection two hours before the first laser treatment as a positive control. Control animals received phosphate-buffered saline (PBS) vehicle. The experiment was terminated 15-25 days later.

Example 16

The blue light model

[0110] Pro-drug *iso*-Butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester is evaluated in the blue light model of retinal degeneration in rats. The drugs is administered continuously with subcutaneous infusion pumps at a dose of 1 mg/kg/day starting two days before blue light exposure. Twenty 4-month old male Sprague Dawley rats (body weight 470-550 g) were used in this study. The animals were exposed to room light on a 12 hour light/12 hour dark cycle before the experiment. All animals were dark adapted overnight (16-20 hours) before blue light. Under the intensity of 6100-6500 lux, rats were exposed to blue light for 4 hours. After the blue light, rats were placed in the dark for another 3 days before returning to normal 12 hour light/12 hour dark. Ocular Coherence Tomography (OCT) measurement was performed at 7 days post blue light exposure. The results demonstrate that blue light exposure with just saline treatment leads to dramatic reduction of retinal thickness measured by OCT, particularly in the superior retina. Histology studies have shown that the reduction in retinal thickness is attributable to loss of photoreceptors. Brimonidine treatment did not prevent the change in retinal thickness while treatment with pro-drug *iso*-Butyric acid 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzyl ester significantly reduced the damage caused by blue light.

REFERENCES CITED IN THE DESCRIPTION

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compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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- Bioreversible Carriers in Drug DesignAmerican Pharmaceutical Association and Pergamon Press19870000 [0027]
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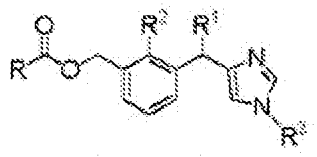
- Handbook of Pharmaceutical SaltsVerlag Helvetica Chimica Acta20020000329-345 [0054]

Patentkrav

1. Sammensætning omfattende en forbindelse med formlen I til anvendelse i en fremgangsmåde til behandling af aldersbetinget makulær degeneration hos en menneskepatient, der har behov for sådan behandling, hvilken omfatter indgivelse af en terapeutisk effektiv mængde af sammensætningen omfattende en forbindelse med formlen I, dens individuelle enantiomerer, dens individuelle diastereoisomerer, dens hydrater, dens solvater, dens krystalformer, dens individuelle tautomerer eller et farmaceutisk acceptabelt salt deraf,



Formel I

hvor

R^1 er H eller C_{1-3}-alkyl;

R^2 er H eller C_{1-3}-alkyl;

R^3 er H, C_{1-10}-alkyl, heterocykel eller aryl; og

R er C_{1-10}-alkyl, heterocykel eller aryl,

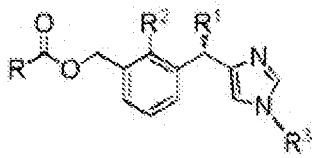
hvor

"alkyl" betyder en mættet monovalent alkandel med lige eller forgrenede alkandele eller kombinationer deraf, som eventuelt kan være substitueret med aminogrupper, arylgrupper, halogener, og en methylen ($-CH_2-$) kan være erstattet med carbonyl, -NH-, carboxyl, amid, svovl eller med oxygen, og

"heterocykel" betyder en aromatisk eller ikke-aromatisk 5 til 10 leddet monocyklisk eller bicyklisk ring indeholdende mindst et heteroatom valgt fra O eller N eller S eller kombinationer deraf, der afbryder den carbocykliske ringstruktur, der eventuelt kan være substitueret med C_{1-6}-alkyl-, amino-, halogen-, -O(C_{1-6} alkyl)-, -OC(O)(C_{1-6} alkyl)-, - C(O)O(C_{1-6} alkyl)-, -NHC(O)(C_{1-6} alkyl)-, -C(O)NH(C_{1-6} alkyl)-, -S(C_{1-6} alkyl)-grupper, og "aryl" betyder en organisk del afledt af et aromatisk carbonhydrid bestående af en monocyklisk eller bicyklisk ring indeholdende 6-10 carbonatomer ved fjernelse af et hydrogenatom, såsom phenyl eller naphthyl, der eventuelt kan være substitueret med, men ikke begrænset til, C_{1-6}-alkyl-, amino-, halogen-, -O(C_{1-6}-alkyl)-, -OC(O)(C_{1-6}-alkyl)-, -

C(O)O(C_{1-6}-alkyl)-, -NHC(O)(C_{1-6}-alkyl)-, -C(O)NH(C_{1-6}-alkyl)- og -S(C_{1-6}-alkyl)-grupper.

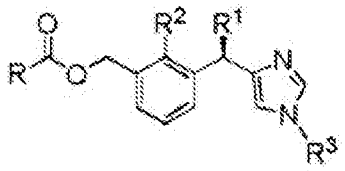
2. Sammensætning til anvendelse ifølge krav 1, hvor forbindelsen har formlen II, dens individuelle diastereoisomerer, dens hydrater, dens solvater, dens krystalformer, dens individuelle tautomerer eller et farmaceutisk acceptabelt salt deraf,



Formel II

hvor R^1, R^2, R^3 og R er som defineret ovenfor.

3. Sammensætning til anvendelse ifølge krav 1, hvor forbindelsen har formlen III, dens individuelle diastereoisomerer, dens hydrater, dens solvater, dens krystalformer, dens individuelle tautomerer eller et farmaceutisk acceptabelt salt deraf,



Formel III

hvor R^1, R^2, R^3 og R er som defineret ovenfor.

4. Sammensætning til anvendelse ifølge krav 2, hvor R^1 er C_{1-3}-alkyl, R^2 er C_{1-3}-alkyl, R^3 er H, og R er C_{1-10}-alkyl.

5. Sammensætning til anvendelse ifølge krav 2, hvor R^1 er methyl, R^2 er methyl, R^3 er H, og R er C_{1-4}-alkyl.

6. Sammensætning til anvendelse ifølge krav 2, hvor forbindelsen er valgt fra:

iso-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;

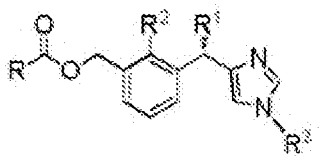
2,2-dimethyl-propionsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;

eddikesyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
benzoesyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
3-phenyl-propionsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2-amino-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2-(2-amino-3-methyl-butyrylamino)-3-methyl-smørsyre 3-[(*S*)-1-(1H-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2-(2-amino-acetylamino)-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester; og
2-amino-3-phenyl-propionsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester.

7. Sammensætning til anvendelse ifølge krav 2, hvor forbindelsen er valgt fra:
iso-smørsyre 3-[(*S*)-1-(1-*iso*-butyryl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2,2-dimethyl-propionsyre 3-{(*S*)-1-[1-(2,2-dimethyl-propionyl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzylester;
eddikesyre 3-[(*S*)-1-(1-acetyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
benzoesyre 3-[(*S*)-1-(1-benzoyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
3-methyl-smørsyre 2-methyl-3-{(*S*)-1-[1-(3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-benzylester;
phenyl-propionsyre 2-methyl-3-{(*S*)-1-[1-(3-phenyl-propionyl)-1*H*-imidazol-4-yl]-ethyl}-benzylester;
2-*tert*-butoxycarbonylamino-3-methyl-smørsyre 3-{(*S*)-1-[1-(2-*tert*-butoxy carbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzylester;
2-*tert*-butoxycarbonylamino-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;

2-(2-*tert*-butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-smørsyre 3-{(*S*)-1-[1-(2-*tert*-butoxycarbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzylester;
2-(2-*tert*-butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2-(2-*tert*-butoxycarbonylamino-acetylamino)-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester; og
2-*tert*-butoxycarbonylamino-3-phenyl-propionsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester.

8. Farmaceutisk sammensætning til anvendelse i en fremgangsmåde til behandling af aldersbetinget makulær degeneration hos en menneskepatient, hvilken sammensætning omfatter en forbindelse med en struktur



Formel II

hvor R^1, R^2, R^3 og R er som defineret ovenfor.

9. Farmaceutisk sammensætning til anvendelse ifølge krav 8, hvor forbindelsen er valgt fra:
iso-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2,2-dimethyl-propionsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
eddikesyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
benzoesyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
3-phenyl-propionsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2-amino-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2-(2-amino-3-methyl-butyrylamino)-3-methyl-smørsyre 3-[(*S*)-1-(1H-imidazol-4-yl)-ethyl]-2-methyl-benzylester;

2-(2-amino-acetylamino)-3-methyl-smørsyre 3-[(*S*)-1-(1H-imidazol-4-yl)-ethyl]-2-methyl-benzylester; og
2-amino-3-phenyl-propionsyre 3-[(*S*)-1-(1H-imidazol-4-yl)-ethyl]-2-methyl-benzylester.

10. Artikel omfattende indpakningsmateriale og et farmaceutisk stof indeholdt i indpakningsmaterialet, hvor det farmaceutiske stof er terapeutisk effektivt til behandling af aldersbetinget makulær degeneration, og hvor indpakningsmaterialet omfatter en mærkat, der indikerer at det farmaceutiske stof kan anvendes til behandling af aldersbetinget makulær degeneration, og hvor det farmaceutiske stof omfatter en effektiv mængde af en forbindelse, dens individuelle diastereoisomerer, dens hydrater, dens solvater, dens krystalformer, dens individuelle isomerer, dens individuelle tautomerer eller et farmaceutisk acceptabelt salt deraf, valgt fra:

iso-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2,2-dimethyl-propionsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
eddikesyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
benzoesyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
3-phenyl-propionsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2-amino-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2-(2-amino-3-methyl-butyrylamino)-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;
2-(2-amino-acetylamino)-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester; og
2-amino-3-phenyl-propionsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester.

11. Artikel omfattende indpakningsmateriale og et farmaceutisk stof indeholdt i indpakningsmaterialet, hvor det farmaceutiske stof er terapeutisk effektivt til behandling af aldersbetinget makulær degeneration, og hvor

indpakningsmaterialet omfatter en mærkat, der indikerer, at det farmaceutiske stof kan anvendes til behandling af aldersbetinget makulær degeneration, og hvor det farmaceutiske stof omfatter en effektiv mængde af en forbindelse, dens individuelle diastereoisomerer, dens hydrater, dens solvater, dens krystalformer, dens individuelle isomerer, dens individuelle tautomerer eller et farmaceutisk acceptabelt salt deraf, valgt fra:

iso-smørsyre 3-[(*S*)-1-(1-*iso*-butyryl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;

2,2-dimethyl-propionsyre 3-{(*S*)-1-[1-(2,2-dimethyl-propionyl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzylester;

eddikesyre 3-[(*S*)-1-(1-acetyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;

benzoesyre 3-[(*S*)-1-(1-benzoyl-1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;

3-methyl-smørsyre 2-methyl-3-{(*S*)-1-[1-(3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-benzylester;

phenyl-propionsyre 2-methyl-3-{(S)-1-[1-(3-phenyl-propionyl)-1*H*-imidazol-4-yl]-ethyl}-benzylester;

2-*tert*-butoxycarbonylamino-3-methyl-smørsyre 3-{(*S*)-1-[1-(2-*tert*-butoxy carbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzylester;

2-*tert*-butoxycarbonylamino-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;

2-(2-*tert*-butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-smørsyre 3-{(*S*)-1-[1-(2-*tert*-butoxycarbonylamino-3-methyl-butyryl)-1*H*-imidazol-4-yl]-ethyl}-2-methyl-benzylester;

2-(2-*tert*-butoxycarbonylamino-3-methyl-butyrylamino)-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester;

2-(2-*tert*-butoxycarbonylamino-acetylamino)-3-methyl-smørsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester; og

2-*tert*-butoxycarbonylamino-3-phenyl-propionsyre 3-[(*S*)-1-(1*H*-imidazol-4-yl)-ethyl]-2-methyl-benzylester.