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(54) Title: NITRIC OXIDE DONATING ISOMANNIDE DERIVATIVES

(57) Abstract: The present invention relates to nitric oxide donating isomannide derivatives, their use for treating glaucoma and ocular hypertension and formulations containing them. The present invention also relates to compositions comprising a nitric oxide donating isomannide derivative and one or more further active ingredients for the use in the treatment of glaucoma and ocular hypertension.



WO 2018/224419 A1

NITRIC OXIDE DONATING ISOMANNIDE DERIVATIVES

Field of the invention

The present invention relates to nitric oxide donating isomannide derivatives, their use for treating glaucoma and ocular hypertension and formulations containing them.

The present invention also relates to compositions comprising a nitric oxide
5 donating isomannide derivative and one or more further active ingredients for the use in the treatment of glaucoma and ocular hypertension.

Background of the invention

Glaucoma is a group of eye disorders leading to progressive damage to the optic nerve, and is characterized by loss of nerve tissue resulting in loss of vision. The most
10 common form of glaucoma, primary open-angle glaucoma, is associated with an increase in the fluid pressure inside the eye. This increase in pressure may cause progressive damage to the optic nerve and loss of nerve fibers. Advanced glaucoma may even cause blindness.

Glaucoma is the second leading cause of blindness in the U.S. It most often occurs in people over age 40, although a congenital or infantile form of glaucoma exists.

15 There are many types of glaucoma. The most common form of glaucoma, primary open-angle glaucoma, develops slowly and usually without any symptoms. It initially affects peripheral or side vision, but can advance to central vision loss. If left untreated, glaucoma can lead to significant loss of vision in both eyes, and may even lead to blindness.

A less common type of glaucoma, acute angle closure glaucoma, usually occurs
20 abruptly due to a rapid increase of pressure in the eye.

Secondary glaucoma occurs as a result of an injury or other eye disease. It may be caused by a variety of medical conditions, physical injuries, and eye abnormalities. Infrequently, eye surgery can be associated with secondary glaucoma.

Normal-tension glaucoma, also known as low-tension glaucoma, is characterized
25 by progressive optic nerve damage and visual field loss with normal intra ocular pressure (IOP) and may account for as many as one-third of the cases of open-angle glaucoma in

U.S. Normal-tension glaucoma is thought to be, in part, due to poor blood flow to the optic nerve, which leads to death of the ganglion cells which carry impulses from the retina to the brain. A pressure lower than normal is necessary to prevent further visual loss.

The most common first line treatment of glaucoma is drug treatment. Several classes
5 of drugs acting by different mechanisms are used as topically administered ocular therapy to lower IOP. These include beta adrenergic blockers (e.g., timolol), topical carbonic anhydrase inhibitors (e.g., dorzolamide), and alpha 2-adrenergic receptor agonists (e.g., brimonidine), all of which act primarily by decreasing the formation of aqueous humor within the eye. Pilocarpine and epinephrine lower IOP in glaucomatous eyes by
10 decreasing the resistance in the trabecular meshwork outflow channels.

Prostaglandin analogues have met an increasing interest for glaucoma therapy as IOP-lowering substances which act primarily by increasing the uveoscleral outflow.

It is known that nitric oxide (NO) has an important role in the eye physiological processes, e.g. regulation of aqueous humor dynamics, vascular tone, retinal
15 neurotransmission, retinal ganglion cell death by apoptosis, phototransduction and ocular immunological responses, on the other hand, the overproduction of NO is involved in several diseases of the eye.

Recently, nitric oxide (NO)-donating prostaglandin F_{2α} analogs have been studied for the reduction of intraocular pressure (IOP)-lowering for the treatment of glaucoma and
20 there are some publications on the studies. For example Valentina Borghi et al., Journal of Ocular Pharmacology and Therapeutics (2010), 26(2), 125-131, and Achim Krauss et al., Experimental Eye Research (2011), 93(3), 250-255 disclose the IOP lower effect of two nitric oxide donating latanoprost acid derivatives that are NCX 125 and BOL-303259-X. The compound known as BOL-303259-X is now in clinical development for the treatment
25 of primary open-angle glaucoma.

US patent 4,590,207 discloses ophthalmic solution containing isosorbide mononitrate as an active ingredient for treating and/or preventing intraocular hypertension and glaucoma.

EP 2 114 398 discloses 2-thio-substituted isosorbide-5-mononitrate derivatives for the treatment of ocular hypertension.

EP 2 238 143 discloses nitric oxide releasing isohexide derivatives that show a potent vasodilatory effect on isolated vessels and systemic hypotensive effect.

5 Intraocular pressure is the primary risk factor for glaucoma and lowering IOP to prevent optic nerve injury is the only proven effective treatment. (Kass MA, et al., Arch Ophthalmol, 2002, 120:701-703; The AGIS Investigators, Am J Ophthalmol, 2000, 130:429- 440), therefore patients with glaucoma need to continue treatment for the rest of their lives. However all the treatments evolved over decades produces a variety of ocular
10 and systemic adverse effects that impact patient compliance. Compliance is of major importance to get the full potential efficacy of the drug treatment.

Accordingly, there is still a need for new drugs for treatments of glaucoma and elevated intra ocular pressure.

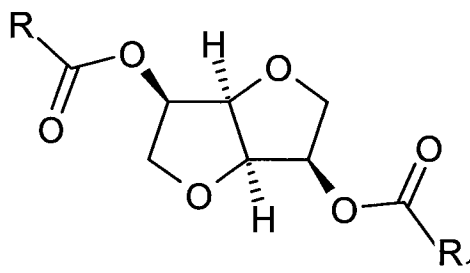
Disclosure of the invention

15 It has now been found novel nitric oxide donating compounds that are efficacious and potent ocular hypotensive agents.

Thus the present invention provides compounds for treating ocular hypertension, glaucoma and disease mediated by elevated intraocular pressure.

An embodiment of the invention relates to compounds of formula (I)

20

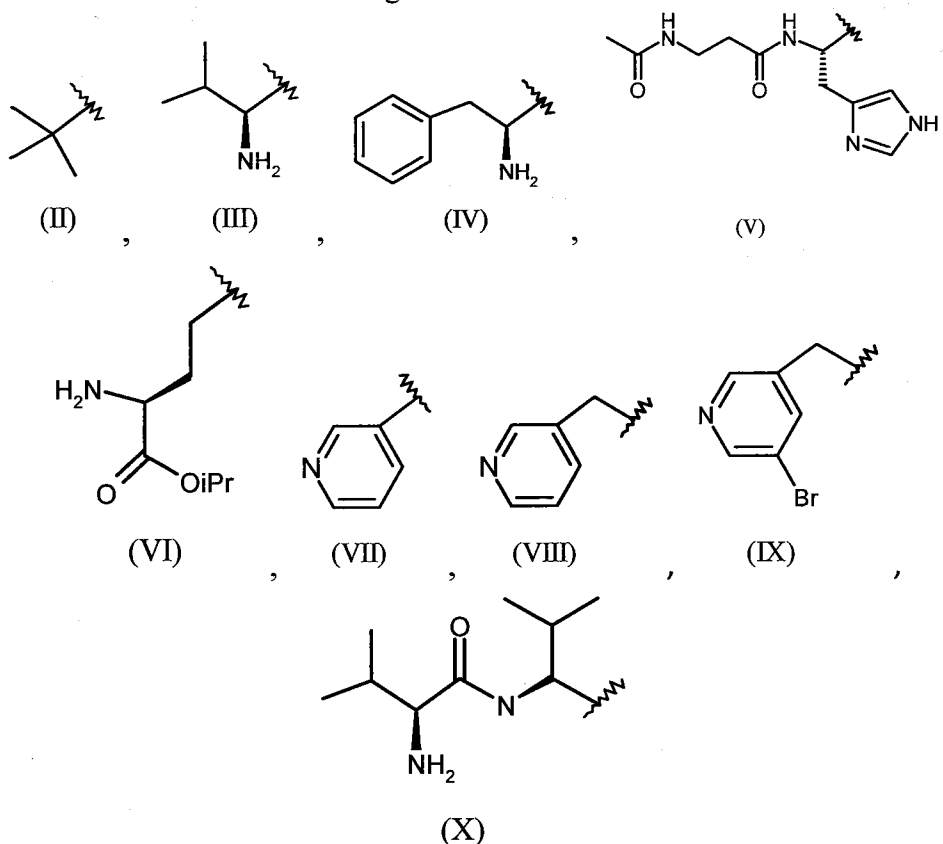


(I)

or a pharmaceutical acceptable salt or stereoisomers thereof,

wherein

R is selected from the following structures:



5 R_1 is $-(CH_2)_m-[O-(CH_2)_n]_p-(CH-ONO_2)_q-CH_2-ONO_2$

wherein

p is 1 or 0;

q is 1 or 0;

m is an integer ranging from 1 to 10; preferably m is from 1 to 6;

10 n is an integer ranging from 1 to 6; preferably n is 1 or 2;

preferred R_1 are selected from the following structures:

(a) $-(CH_2)_3-(CH-ONO_2)-CH_2-ONO_2$,

(b) $-(CH_2)_4-CH_2-ONO_2$,

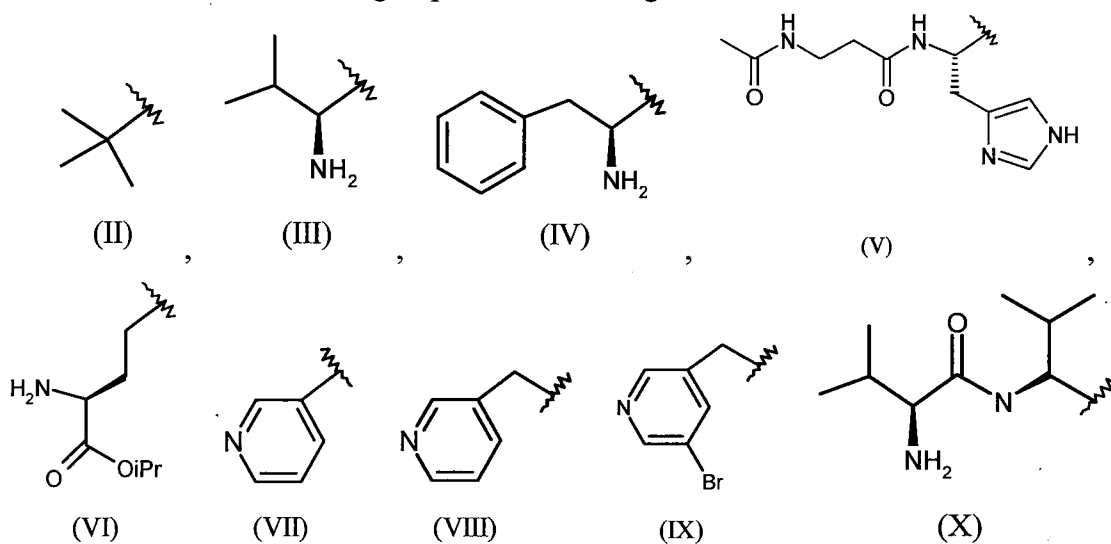
(c) $-(CH_2)-O-(CH_2)-CH_2-ONO_2$ or

15 (d) $-(CH_2)_2-O-(CH_2)-(CH-ONO_2)-CH_2-ONO_2$.

Another embodiment of the invention relates to compounds of formula (I) or a pharmaceutical acceptable salt or stereoisomers thereof,

wherein:

R is selected from the group of the following structures:



R_1 is $-(CH_2)_m-[O-(CH_2)_n]_p-(CH-ONO_2)_q-CH_2-ONO_2$

5

wherein

p is 0;

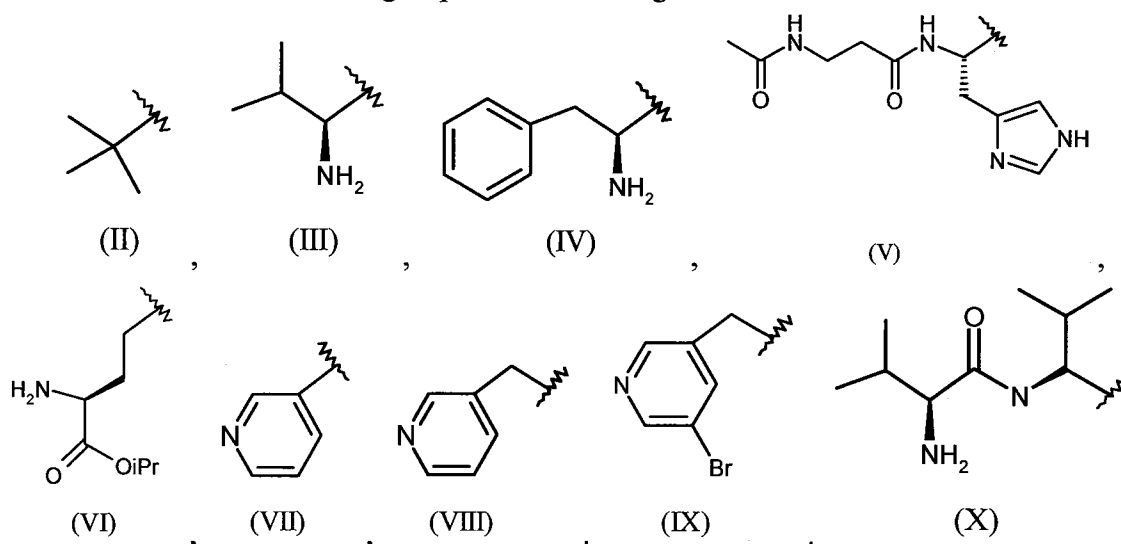
q is 0;

and m is from 1 to 6;

Another embodiment of the invention relates to compounds of formula (I) or a
10 pharmaceutical acceptable salt or stereoisomers thereof,

wherein:

R is selected from the group of the following structures:



15

R_1 is $-(CH_2)_m-[O-(CH_2)_n]_p-(CH-ONO_2)_q-CH_2-ONO_2$

wherein

p is 0;

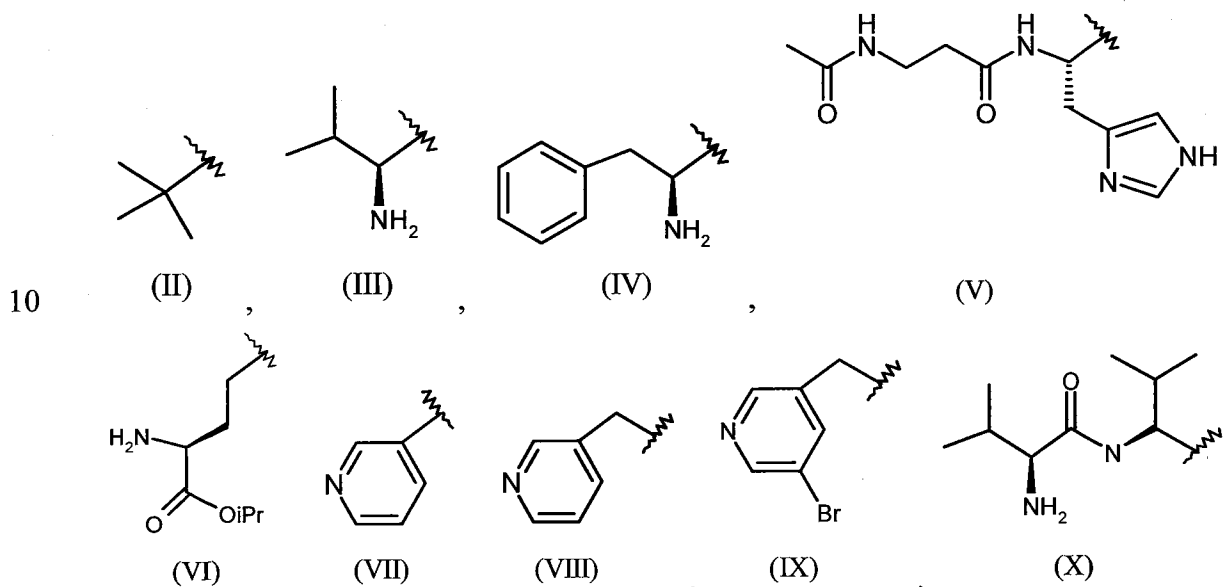
q is 1;

m is from 1 to 6.

5 Another embodiment of the invention relates to compounds of formula (I) or a pharmaceutical acceptable salt or stereoisomers thereof,

wherein:

R is selected from the group of the following structures:



R_1 is $-(CH_2)_m-[O-(CH_2)_n]_p-(CH-ONO_2)_q-CH_2-ONO_2$

wherein

p is 1;

15 q is 0 or 1;

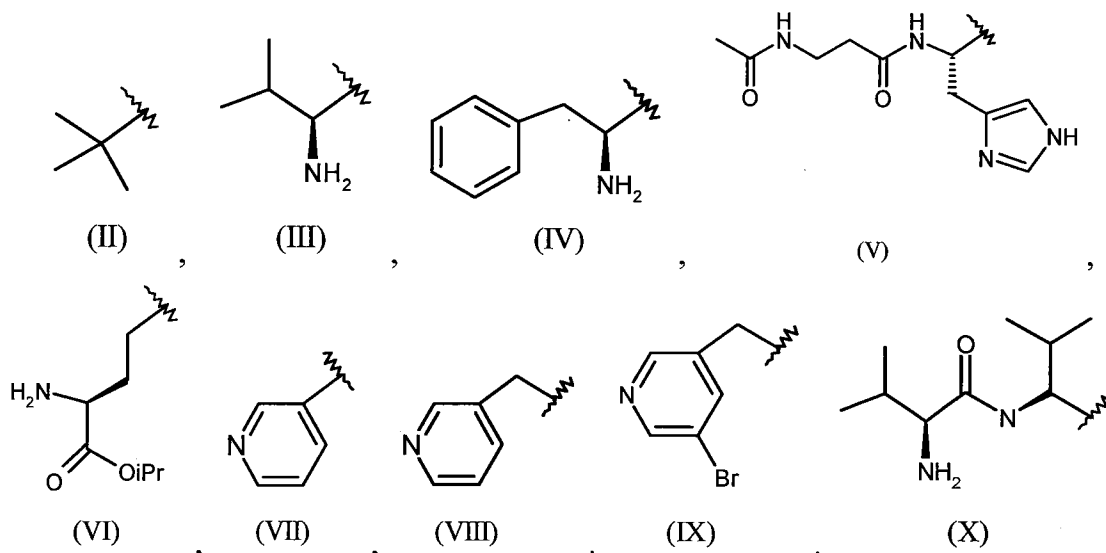
m is from 1 to 6;

n is 1 or 2.

Another embodiment of the invention relates to compounds of formula (I) or a pharmaceutical acceptable salt or stereoisomers thereof,

20 wherein:

R is selected from the group of the following structures:



and R_1 are selected from the following structures:

(a) $-(CH_2)_3-(CH-ONO_2)-CH_2-ONO_2$,

(b) $-(CH_2)_4-CH_2-ONO_2$,

(c) $-(CH_2)-O-(CH_2)-CH_2-ONO_2$ or

(d) $-(CH_2)_2-O-(CH_2)-(CH-ONO_2)-CH_2-ONO_2$.

Another embodiment of the invention includes compounds of formula (I) or a pharmaceutical acceptable salt or stereoisomers thereof,

wherein:

R is



(II)

R_1 is $-(CH_2)_m-[O-(CH_2)_n]_p-(CH-ONO_2)_q-CH_2-ONO_2$

wherein

p is 0;

q is 0;

and m is from 1 to 6.

Another embodiment of the invention includes compounds of formula (I) or a pharmaceutical acceptable salt or stereoisomers thereof,

wherein:

R is



(II)

R_1 is $-(CH_2)_m-[O-(CH_2)_n]_p-(CH-ONO_2)_q-CH_2-ONO_2$

wherein

5 p is 0;

q is 1;

m is from 1 to 6.

Another embodiment of the invention includes compounds of formula (I) or a pharmaceutical acceptable salt or stereoisomers thereof,

10 wherein:

R is



(II)

R_1 is $-(CH_2)_m-[O-(CH_2)_n]_p-(CH-ONO_2)_q-CH_2-ONO_2$

wherein

15 wherein

p is 1;

q is 0 or 1;

m is from 1 to 6;

n is 1 or 2.

20 Another embodiment of the invention includes compounds of formula (I) wherein:

R is



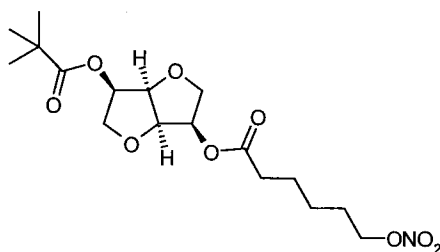
(II)

and R_1 are selected from the following structures:

- (a) $-(\text{CH}_2)_3-(\text{CH}-\text{ONO}_2)-\text{CH}_2-\text{ONO}_2$,
 (b) $-(\text{CH}_2)_4-\text{CH}_2-\text{ONO}_2$,
 (c) $-(\text{CH}_2)-\text{O}-(\text{CH}_2)-\text{CH}_2-\text{ONO}_2$ or
 (d) $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)-(\text{CH}-\text{ONO}_2)-\text{CH}_2-\text{ONO}_2$.

5 Another embodiment of the invention includes compounds with structures of formulae (1) to (15) as reported below, or a pharmaceutical acceptable salt or stereoisomers thereof:

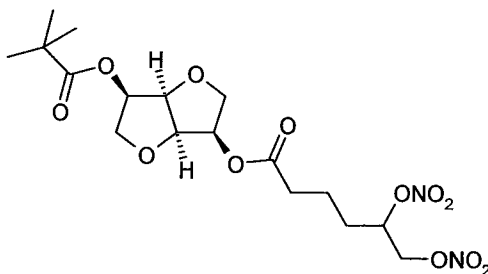
(3R,3aR,6R,6aR)-6-(pivaloyloxy)hexahydrofuro[3,2-b]furan-3-yl 6-(nitrooxy)hexanoate
 (Compound (1))



10

(1)

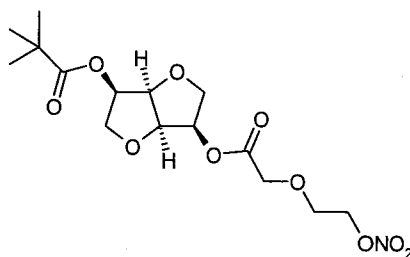
(3R,3aR,6R,6aR)-6-(pivaloyloxy)hexahydrofuro[3,2-b]furan-3-yl
 5,6-bis(nitrooxy)hexanoate (Compound (2))



15

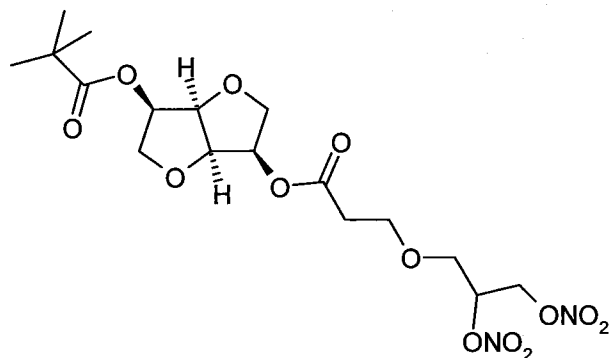
(2)

(3R,3aR,6R,6aR)-6-(2-(2-(nitrooxy)ethoxy)acetoxy)hexahydrofuro[3,2-b]furan-3-yl
 pivalate (Compound (3))



(3)

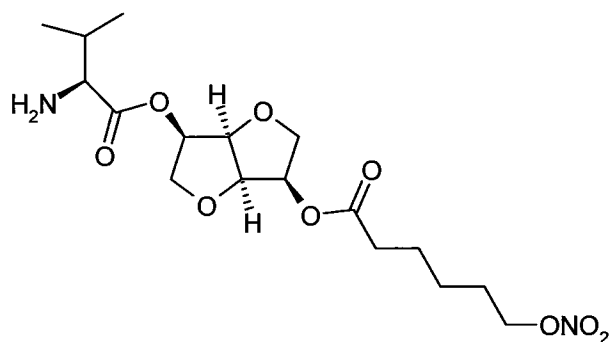
(3R,3aR,6R,6aR)-6-(3-(2,3-bis(nitrooxy)propoxy)propanoyloxy)hexahydrofuro[3,2-b]furan-3-yl pivalate (Compound (4))



5

(4)

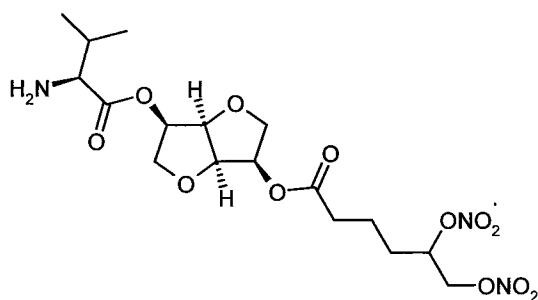
(3R,3aR,6R,6aR)-6-((S)-2-amino-3-methylbutanoyloxy)hexahydrofuro[3,2-b]furan-3-yl 6-(nitrooxy)hexanoate (Compound (5))



10

(5)

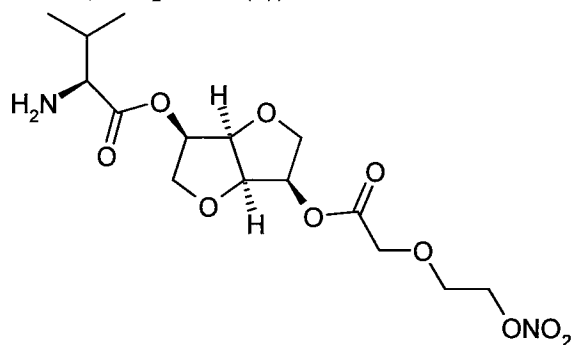
(3R,3aR,6R,6aR)-6-((S)-2-amino-3-methylbutanoyloxy)hexahydrofuro[3,2-b]furan-3-yl 5,6-bis(nitrooxy)hexanoate (Compound (6))



15

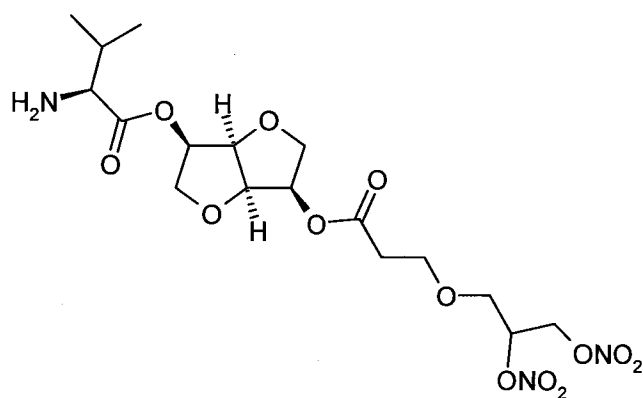
(6)

(S)-((3R,3aR,6R,6aR)-6-(2-(2-(nitrooxy)ethoxy)acetoxy)hexahydrofuro[3,2-b]furan-3-yl)
2-amino-3-methylbutanoate (Compound (7))



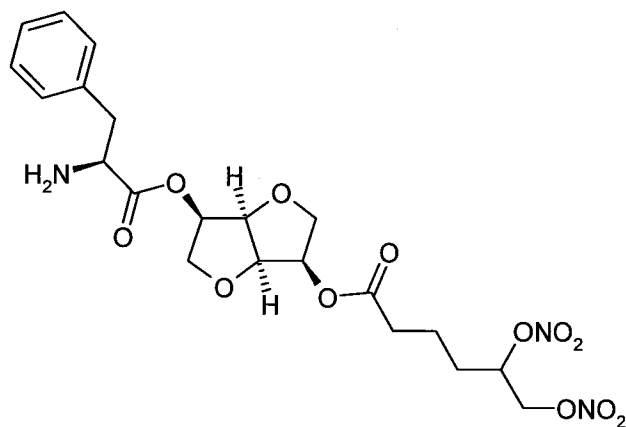
(7)

5 (2S)-((3R,3aR,6R,6aR)-6-(3-(2,3-bis(nitrooxy)propoxy)propanoyloxy)
hexahydrofuro[3,2-b]furan-3-yl) 2-amino-3-methylbutanoate (Compound (8))



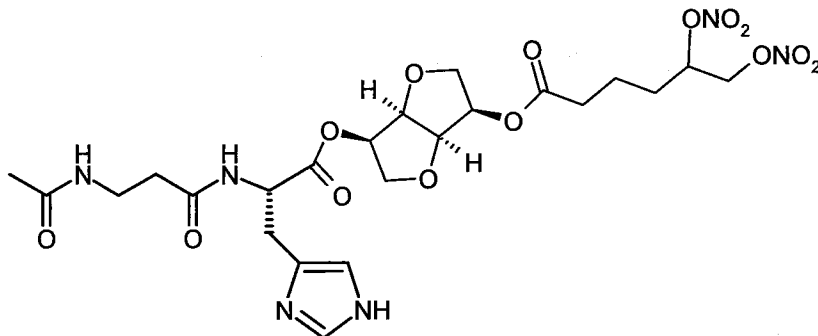
(8)

10 (3R,3aR,6R,6aR)-6-((S)-2-amino-3-phenylpropanoyloxy)hexahydrofuro[3,2-b]furan-3-yl
5,6-bis(nitrooxy)hexanoate (Compound (9))



(9)

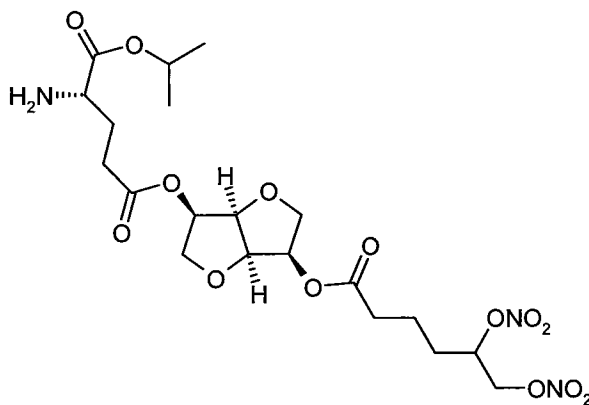
(3R,3aR,6R,6aR)-6-((S)-2-(3-acetamidopropanamido)-3-(1H-imidazol-5-yl)propanoyloxy)hexahydrofuro[3,2-b]furan-3-yl 5,6-bis(nitrooxy)hexanoate (Compound (10))



5

(10)

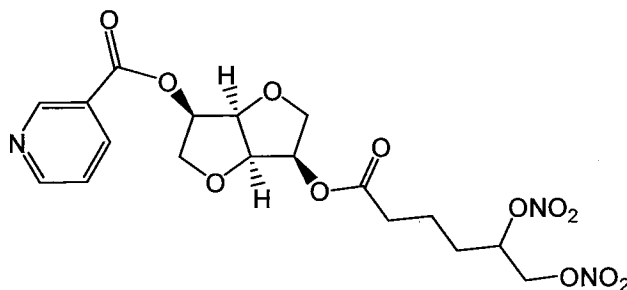
(2S)-5-((3R,3aR,6R,6aR)-6-(5,6-bis(nitrooxy)hexanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 1-isopropyl 2-aminopentanedioate (Compound (11))



10

(11)

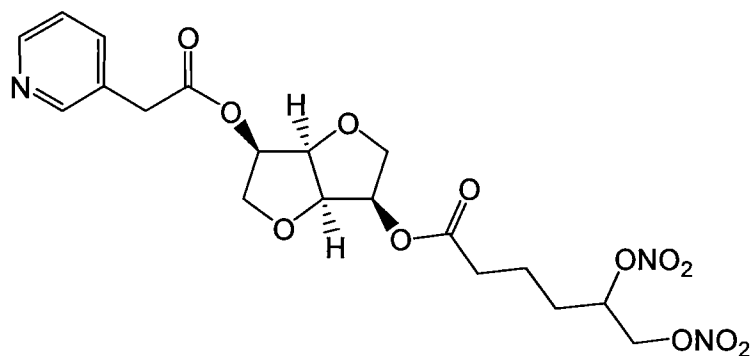
(3R,3aR,6R,6aR)-6-(5,6-bis(nitrooxy)hexanoyloxy)hexahydrofuro[3,2-b]furan-3-yl nicotinate (Compound (12))



15

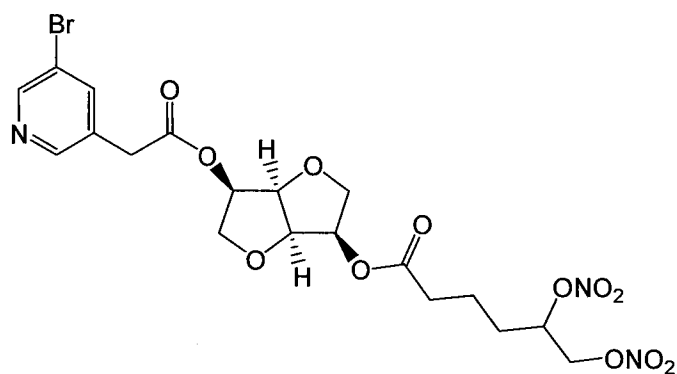
(12)

(3R,3aR,6R,6aR)-6-(2-(pyridin-3-yl)acetoxy)hexahydrofuro[3,2-b]furan-3-yl 5,6-bis(nitrooxy)hexanoate (Compound (13))



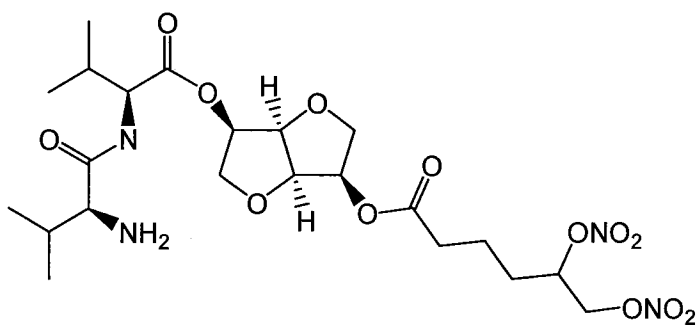
5 (13)

(3R,3aR,6R,6aR)-6-(2-(5-bromopyridin-3-yl)acetoxy)hexahydrofuro[3,2-b]furan-3-yl 5,6-bis(nitrooxy)hexanoate (Compound (14))



10 (14)

(3R,3aR,6R,6aR)-6-((S)-2-((S)-2-amino-3-methylbutanamido)-3-methylbutanoyloxy)hexahydrofuro[3,2-b]furan-3-yl 5,6-bis(nitrooxy)hexanoate (Compound (15))



15 (15)

The compounds of formula (I) have an improved IOP-reducing efficacy and a prolonged IOP effect as compared to the known nitric oxide donating compounds.

Certain specific compounds of the present invention contain a basic group that allows the compounds to be converted into acid salts. Thus the compounds of the present invention may exist as salts. Example of such salts includes hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; or an organic acid such as for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, fumaric acid, maleic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pantoic acid, citric, methylsulfonic, ethanesulfonic, benzenesulfonic, formic and the like.

Included within the scope of the present invention are the individual enantiomers of the compounds of formula (I), as well as their diastereoisomers, racemic and non-racemic mixtures.

Another embodiment provides the use of compounds of formula (I) for treating ocular hypertension or drug-induced ocular hypertension.

Another embodiment provides the use of the compounds of formula (I) for treating glaucoma in particular primary open angle glaucoma, normal intraocular tension glaucoma, pseudoexfoliation glaucoma, acute angle-closure glaucoma, chronic closed angle glaucoma.

Another embodiment of the invention relates to a composition comprising a compound of formula (I) and at least another active agent selected from the following classes of drugs:

Beta-adrenergic antagonists wherein the beta-adrenergic antagonist is selected from: carteolol, levobunolol, metipranolol or timolol hemihydrate;

Prostaglandin analogues wherein the prostaglandin analogue is selected from: latanoprost, travoprost, tafluprost or bimatoprost;

Adrenergic agonists wherein the adrenergic agonist is selected from: epinephrine borate, epinephrine hydrochloride, dipivefrin or apraclonidine;

Carbonic anhydrase inhibitors wherein the carbonic anhydrase inhibitor is selected from acetazolamide, dichlorphenamide, methazolamide, brinzolamide or dorzolamide;

Cholinergic agonists wherein the cholinergic agonist is selected from carbachol, pilocarpine hydrochloride, pilocarpine nitrate or pilocarpine;

5 Steroids wherein the steroid is selected from fluocinolone, fluticasone propionate, triamcinolone or dexamethasone;

Cholinesterase inhibitors wherein the cholinesterase inhibitor is selected from demecarium, echothiophate or physostigmine.

Another embodiment of the invention provides a composition which is a kit
10 comprising a topical ocular dosage form comprising a compound of formula (I) or salts thereof and another topical ocular dosage form comprising an active agent selected from the following classes of drugs: prostaglandin analogues, beta-adrenergic antagonists, carbonic anhydrase inhibitors, cholinergic agonists, steroids or cholinesterase inhibitors.

Another embodiment provides the use of the compositions comprising compound
15 of formula (I) and at least another active agent reported above for treating ocular hypertension.

Another embodiment provides the use of the compositions comprising a compound of formula (I) and at least another active agent reported above for treating glaucoma in particular primary open angle glaucoma, normal intraocular tension glaucoma,
20 pseudoexfoliation glaucoma, acute angle-closure glaucoma, chronic closed angle glaucoma.

Another embodiment of the invention provides a compound of formula (I) for use in the treatment of ocular hypertension and glaucoma wherein the compound of formula (I) is simultaneously, separately or sequentially administered with another active agent
25 selected from the following classes of drugs: prostaglandin analogues, beta-adrenergic antagonists carbonic anhydrase inhibitors, cholinergic agonists, steroids or cholinesterase inhibitors.

The compounds of formula (I) and their compositions may be provided as part of a

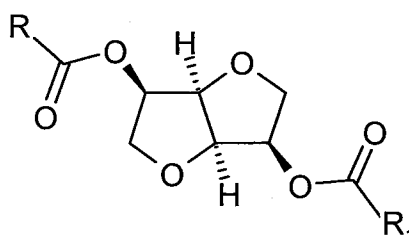
pharmaceutical compositions as described therein.

In the compositions for topical administration, the compounds of the present invention are generally formulated as between 0.0003% to 3% (w/v) solutions in water at a pH from 4.5 to 8.0. The compounds are preferably formulated as between 0.003 to 1% (w/v) and, most preferably between 0.03% to 1% (w/v).

In another aspect, there is provided a topical ocular pharmaceutical composition comprising a compound of formula (I) or salts thereof and a pharmaceutically acceptable excipient. Acceptable excipients may include preservatives, dissolving agents and viscosity agents.

General synthesis

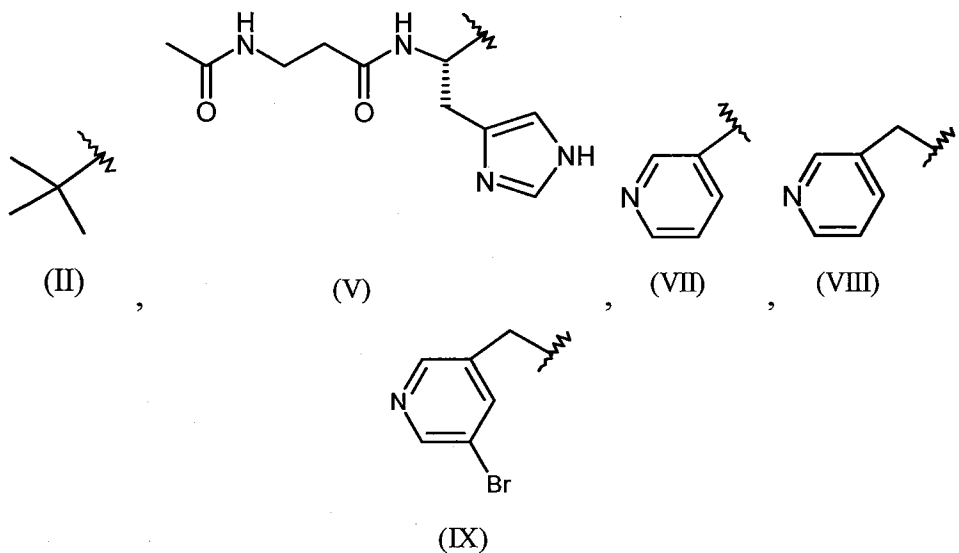
Compounds of formula (I)



(I)

wherein

R is selected from the following structures:

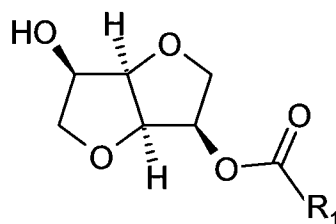


R_1 is $-(CH_2)_m-[O-(CH_2)_n]_p-(CH-ONO_2)_q-CH_2-ONO_2$

wherein p is 1 or 0 and q is 1 or 0; m is an integer ranging from 1 to 10; n is an integer ranging from 1 to 6,

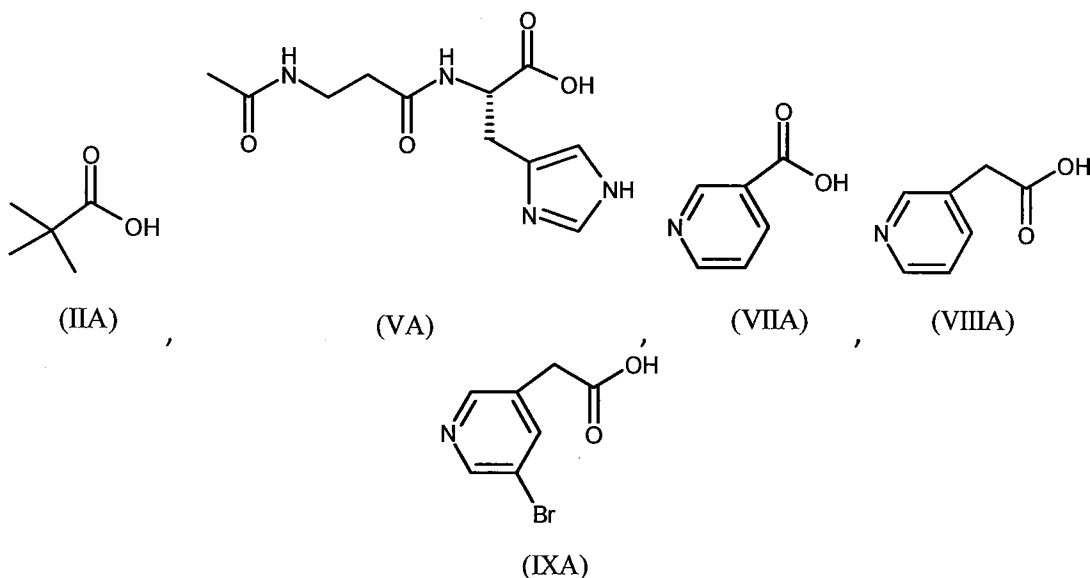
are prepared by reacting compound of formula (Ia)

5



(Ia)

with a compound of formula (IIA), (VA), (VIIA)-(IXA)



10

(IIA)

(VA)

(VIIA)

(VIIIa)

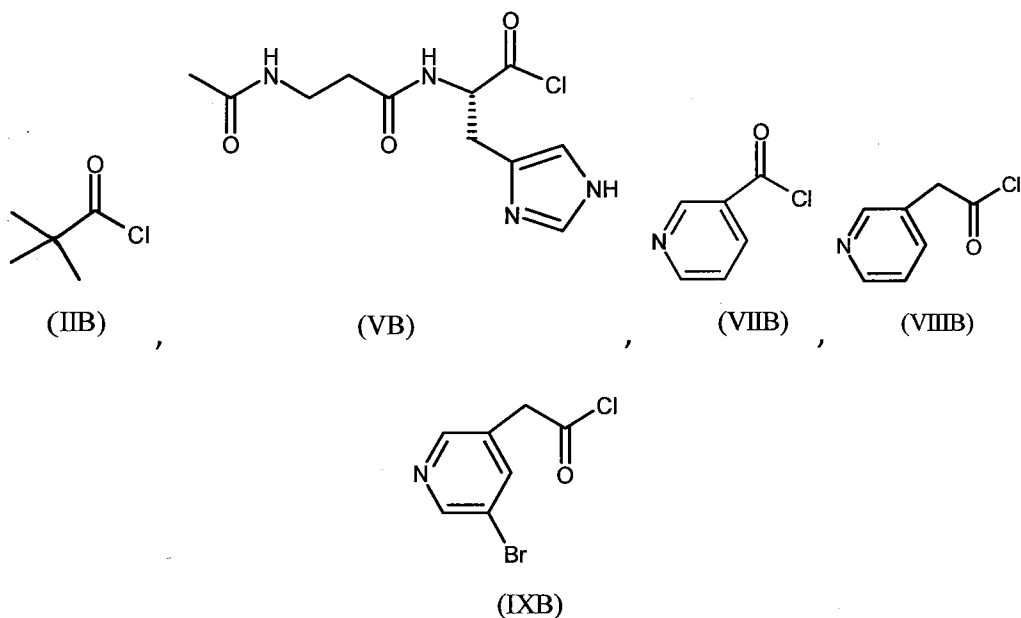
(IXA)

15

in presence of a coupling agent such as N,N' -dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC), O-(benzotriazol-1-yl)- N,N,N',N' -tetramethyluronium hexafluorophosphate (HBTU) or 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide-hexafluorophosphate (HATU) and of catalytic amount of dimethylaminopyridine (DMAP), in a aprotic polar/non polar solvent such as tetrahydrofuran (THF), dimethylformamide (DMF) or CH_2Cl_2 , at temperature ranging from $0^\circ C$ to $80^\circ C$.

Alternatively, compound of formula (Ia) is reacted with a compound of formulae

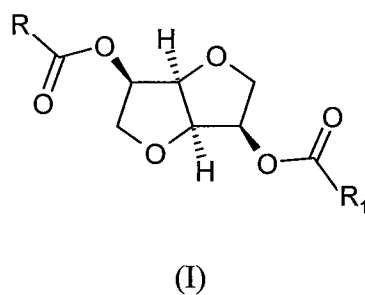
(IIB), (VB), (VIIB)-(IXB)



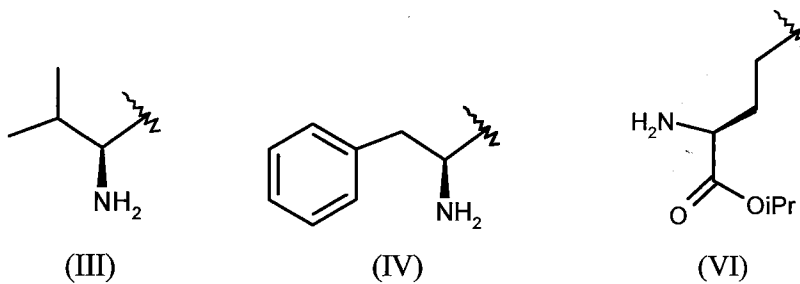
5

in presence of an organic or inorganic base such as triethylamine (TEA), DMAP or Na_2CO_3 in presence or not of catalytic amount of DMAP, in a aprotic polar/non polar solvent such as acetonitrile, DMF, methyl tert-butyl ether (MTBE) or CH_2Cl_2 , at temperature ranging from 0°C to 80°C .

10 Compound of formula (I)

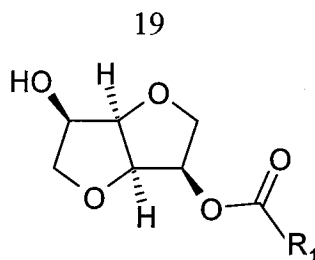


wherein R is selected from the following structures:



15

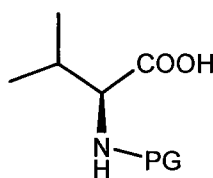
and R_1 is as defined above are prepared by reacting compound of formula (Ia)



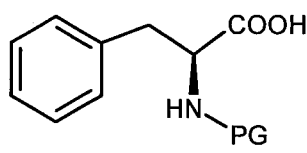
(Ia)

with a compound of formula (IIIC), (IVC) or (VIC), wherein PG is an amino protective group such as the BOC group:

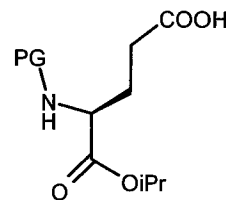
5



(IIIC)



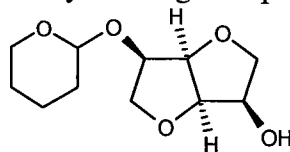
(IVC)



(VIC)

The reaction is carried out in an aprotic polar/non polar solvent such as THF, DMF or CH₂Cl₂, in presence of N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate (HBTU) or 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide-hexafluorophosphate (HATU), or other coupling reagents, in presence of catalytic amount of DMAP at temperature ranging from 0°C to 80°C, eventually deprotecting the amino group with acid hydrolysis as known in the art (see T.W. Greene, P. G. M. Wuts "Protective groups in organic Synthesis", 4th edition, J. Wiley & Sons, New York, 2006).

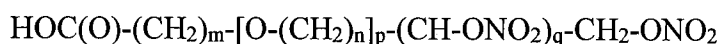
Compounds (Ia) are prepared by reacting Compound (Ib)



(Ib)

with a compound of formula R₁-COOH having the following structure

20



wherein p is 1 or 0 and q is 1 or 0; m is an integer ranging from 1 to 10; n is an

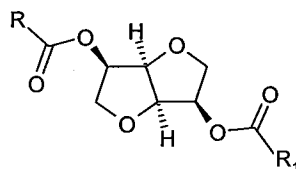
integer ranging from 1 to 6. The reaction is carried out in an aprotic polar/non polar solvent such as THF, DMF or CH₂Cl₂, in presence of N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate (HBTU) or
 5 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide-hexafluorophosphate (HATU), or other coupling reagents, in presence of catalytic amount of DMAP at temperature ranging from 0°C to 80°C.

Intermediate compound (Ib) is prepared by reacting 1,4:3,6-dianhydro-D-mannitol with 3,4-dihydro-2H-pyran in the presence of a catalytic amount of p-toluenesulfonic acid.
 10 Details of the reaction procedure and purification of Intermediate (Ib) are disclosed in Example 1, Step 6.

Compounds of formula R₁-COOH can be prepared according to known methods.

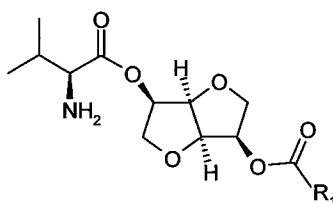
Compounds of formula (IIA), (VA), (VIIA)-(IXA), (IIB), (VB), (VIIB)-(IXB), (IIIC), (IVC) and (VIC) are commercially available.

15 Compound of formula (I)



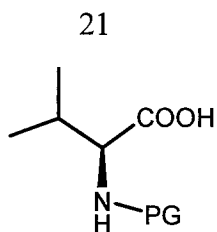
(I)

wherein R is the structures (X) and R₁ are as defined above can be generally
 20 prepared by reacting compound of formula (I) wherein R is the structure (III)



(I)

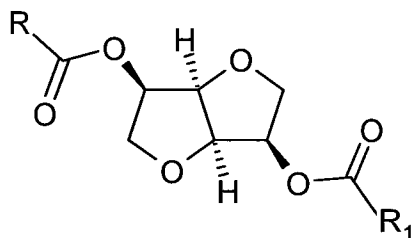
with a commercially available compound of formula C1 wherein PG is an amino
 25 protective group such as the BOC group as already described:



C1

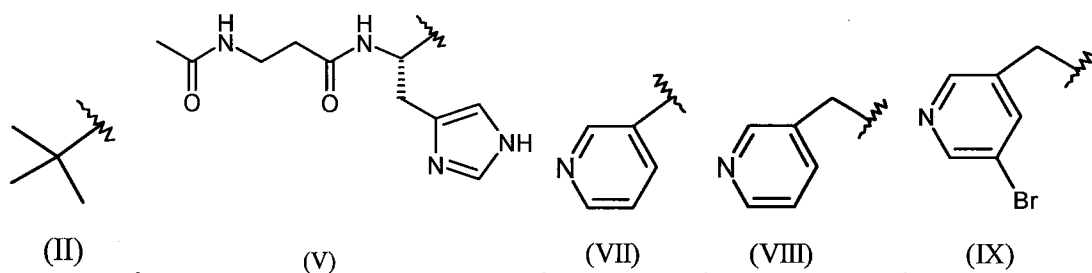
The reaction is carried out in an aprotic polar/non polar solvent such as THF, DMF or CH_2Cl_2 , in presence of N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) or 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), or other coupling reagents, in presence of catalytic amount of DMAP at temperature ranging from 0°C to 80°C , eventually deprotecting the amino group with acid hydrolysis as known in the art (see T.W. Greene, P. G. M. Wuts "Protective groups in organic Synthesis", 4th edition, J. Wiley & Sons, New York, 2006).

Alternatively Compounds of formula (I)

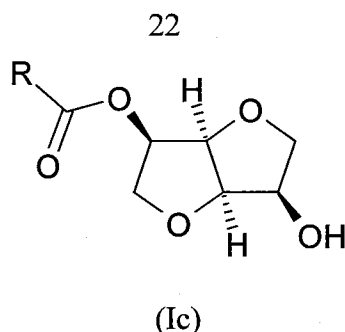


(I)

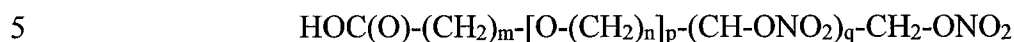
wherein R_1 is as above defined and R is selected from the following structures:



can be prepared by reacting a compound of formula (Ic)

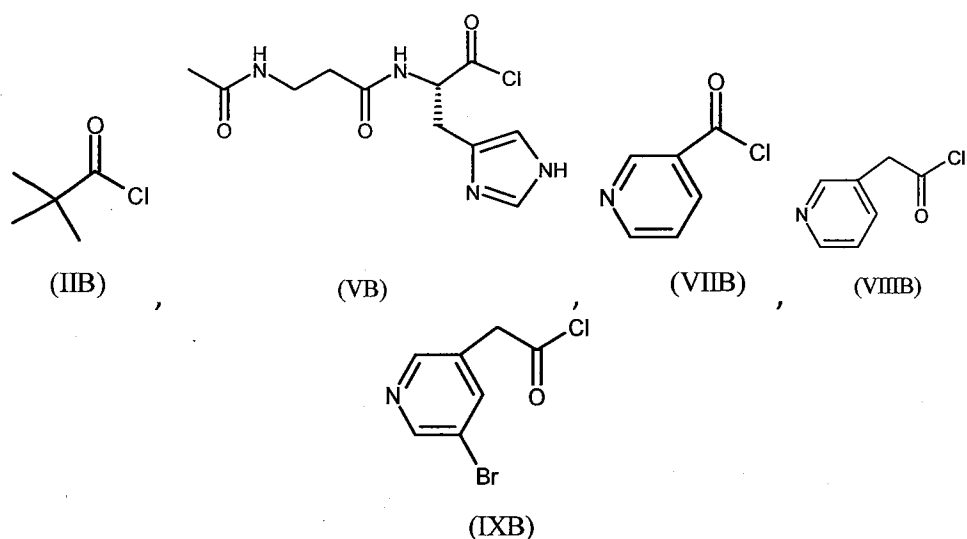


wherein R is as above defined with a compound of formula $R_1\text{-COOH}$ reported below



wherein p is 1 or 0 and q is 1 or 0; m is an integer ranging from 1 to 10; n is an integer ranging from 1 to 6. The reaction is carried out in an aprotic polar/non polar solvent such as THF, DMF or CH_2Cl_2 , in presence of N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) or 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), or other coupling reagents, in presence of catalytic amount of DMAP at temperature ranging from 0°C to 80°C .

Intermediate compound (Ic) is prepared by reacting 1,4:3,6-dianhydro-D-mannitol
15 with the appropriate compound of formula (IIB), (VB), (VIIB)-(IXB):

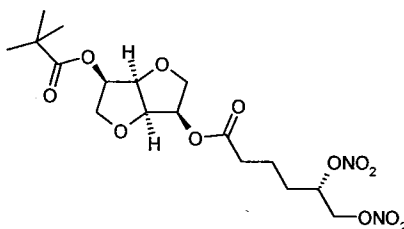


in presence of an organic or inorganic base such as triethylamine (TEA), DMAP
20 or Na_2CO_3 in presence or not of catalytic amount of DMAP, in a aprotic polar/non polar

solvent such as acetonitrile, DMF, methyl tert-butyl ether (MTBE) or CH₂Cl₂, at temperature ranging from 0°C to 80°C.

Example 1

Synthesis of (S)-((3R,3aR,6R,6aR)-6-(pivaloyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (corresponding to compound (2) (S)-isomer)



(2)

Step 1: Synthesis of Hex-5-enyl-4-nitrobenzoate

To a stirred solution of hex-5-enol (21.25 g, 200 mmol) and 4-nitrobenzoyl chloride (37.11 g, 200 mmol) in dichloromethane (300 mL) at 0°C, triethylamine (28 mL, 200 mmol) was added. The reaction was stirred at RT for 4 h and then washed with water, HCl 1M, water and brine. The solvent was removed under reduced pressure to give a crude oil which was treated with n-hexane to give a solid that was filtered off. The mother liquor was evaporated to give the title compound as yellow oil (41 g, 82%).

MS: $m/z = 250$ [M+H]⁺

TLC: DCM 100% R_f = 0.4

Step 2: synthesis of (5S)- 5,6-dihydroxyhexyl 4-nitrobenzoate.

A solution of AD-Mix α (50 g) in a mixture tBuOH /H₂O (227 mL each) was stirred for 10 min at room temperature and then cooled to 4°C. After 15 min, hex-5-enyl 4-nitrobenzoate (Step 1) (8.8 g, 35.5 mmol) was added and the reaction stirred overnight at 4°C. Then ethyl acetate (200 mL) was added, followed by careful addition of sodium metabisulfite (12 g). The reaction was left for 30 min at 4°C and then treated with water (200 mL). The aqueous phase extracted twice with ethyl acetate (2 x 100 mL). The combined organic phases were washed with water and brine, dried over sodium sulfate, evaporated to give a white solid. The solid was suspended in diethyl ether (100 mL) and

stirred overnight to give the title compound as white solid (8.1 g, 84%).

MS: 284 $[M+H]^+$

TLC: (DCM/ MeOH-0,5 %) $R_f = 0.36$

Step 3: synthesis of (5S)-5,6-bis(nitrooxy)hexyl 4-nitrobenzoate.

5 To a stirred solution of fuming nitric acid (3.6 mL, 88 mmol) in dichloromethane (3 mL) at 0°C, acetic anhydride (13.7 mL) was added and, after 10 minutes of stirring, a solution of (5S)-5,6-dihydroxyhexyl 4-nitrobenzoate (Step 2) (5 g, 17.6 mmol) in dichloromethane (2 mL) was added. The reaction was stirred for 60 min. The crude mixture was poured on crushed ice and the organic layer extracted, washed with water, brine, dried
10 over sodium sulfate, evaporated to give the title compound as pale yellow oil (6.4 g, 99%) used in the next step without further purification.

MS: 374 $[M+H]^+$

TLC: (DCM 100 %) $R_f = 0.37$

Step 4: Synthesis of (2S)-6-hydroxy-2-(nitrooxy)hexyl nitrate.

15 To a stirred solution of (5S)-5,6-bis(nitrooxy)hexyl 4-nitrobenzoate (Step 3) (7.4 g, 19.82 mmol) in a 1/1 mixture of ethanol /THF (33 mL of each) at 0°C, a 2 M sodium hydroxide solution (19.8 mL, 2 eq) was added and the reaction was stirred for 2 h. The reaction was diluted with ethyl acetate and water (100 mL of each). The organic layer was washed with water and brine, dried over sodium sulfate and evaporated. The oily residue
20 was purified by column chromatography (gradient system from 40/60 ethyl acetate/Cy to 60/40 ethyl acetate/Cy) to give the title compound as colorless oil (4.1 g, 92%).

TLC: (EtOAc/ Cy-50 %) $R_f = 0.31$

Step 5: synthesis of (5S)-5,6-bis(nitrooxy)hexanoic acid.

To a solution of (2S)-6-hydroxy-2-(nitrooxy)hexyl nitrate (Step 4) (3 g, 13.4 mmol)
25 and Sodium periodate (8.4 g, 40.2 mmol) in $CHCl_3$, Acetonitrile, H_2O (1:1:1), ruthenium (IV) oxide (180 mg, 1.34 mmol) was added. The mixture was stirred overnight at RT, the precipitate was filtered off and the solvent was removed under reduced pressure. The residue was dissolved in DCM, washed with water, dried with $MgSO_4$, filtered and

concentrated under reduced pressure. The crude was purified by flash chromatography (EtOAc in cyclohexane from 5% to 50%) affording 2.4 g of (5S)-5,6-bis(nitrooxy)hexanoic acid (Yield: 75%)

TLC: (DCM/ MeOH-0,5 %) R_f = 0.34

5 **Step 6:** Synthesis of (3R,3aR,6R,6aR)-6-(tetrahydro-2H-pyran-2-yloxy)hexahydrofuro[3,2-b]furan-3-ol.

To a solution of 1,4:3,6-dianhydro-D-mannitol (5.00 g, 34.2 mmol) in DCM (102 mL) 3,4-dihydro-2H-pyran (3.88 mL, 42.8 mmol) was added, followed by p-toluenesulfonic acid (65 mg, 1.34 mmol). The reaction mixture was stirred at rt for 16
10 hrs. The solution was washed with brine, the organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by flash chromatography (Biotage SP1, EtOAc/n-hexane from 30 to 100%), affording the title product as pale yellow oil.

Step 7: Synthesis of (5S)-((3R,3aR,6R,6aR)-6-(tetrahydro-2H-pyran-2-yloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate
15

To a solution of (3R,3aR,6R,6aR)-6-(tetrahydro-2H-pyran-2-yloxy)hexahydrofuro[3,2-b]furan-3-ol (2.96 g, 12.9 mmol) in DCM (40.8 mL) a solution of the crude (S)-5,6-di(nitrooxy)hexanoic acid (3.06 g, 12.85 mmol) (Step D) in DCM (9.15 mL) was added followed by EDAC (3.69 g, 19.28 mmol) and
20 4-dimethylaminopyridine (175 mg, 1.28 mmol). The reaction mixture was stirred at rt for 16.5 hrs. The solvent was removed under reduced pressure. The crude residue was purified by flash chromatography (Biotage SP1, EtOAc/n-hexane from 10 to 60%), affording the title product as pale yellow oil.

Step 8: Synthesis of (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-
25 3-yl) 5,6-bis(nitrooxy)hexanoate.

To a solution of (5S)-((3R,3aR,6R,6aR)-6-(tetrahydro-2H-pyran-2-yloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (2.27 g, 5.04 mmol) in ethanol (40 mL) pyridinium p-toluenesulfonate (127 mg, 0.504 mmol) was added. The

reaction mixture was stirred at 45°C for 4 hrs. The reaction mixture was filtered, concentrated under reduced pressure. The crude residue was purified by flash chromatography (Biotage SP1, EtOAc/n-hexane from 10 to 60%), affording the title product as pale yellow oil.

- 5 ¹H-NMR ((300 MHz, CDCl₃): δ 5.30 (1H, dd), 5.16 (1H, q), 4.77 (1H, d), 4.71 (1H, t), 4.50 (2H, m), 4.26 (1H, m), 4.12 (1H, dd), 3.94 (1H, dd), 3.85 (1H, dd), 3.58 (1H, dd), 2.61 (1H, d), 2.47 (2H, m), 1.83 (4H, m).

Step 9: Synthesis of (S)-((3R,3aR,6R,6aR)-6-(pivaloyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate ((S)-isomer of Compound (2)).

- 10 To a solution of (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (150 mg, 0.410 mmol) in dry DCM (3 ml), triethylamine (0.057 ml, 0.410 mmol) and trimethylacetyl chloride (0.076 ml, 0.614 mmol) were added.

- The mixture was stirred 5 days at room temperature, checking the conversion by LC-MS. During this time, other 4.5 equiv. (0.228 ml, 1.842 mmol) of trimethylacetyl
15 chloride were added.

- Once the conversion was complete, the mixture was diluted with DCM and water was added. The two phases were separated and the aqueous phase extracted twice with DCM. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (isocratic elution
20 cyclohexane/ethyl acetate 85:15), affording 81 mg of the desired product (yield: 44%).

¹H NMR (600 MHz, DMSO-d₆) δ 5.46 – 5.40 (m, 1H), 5.01 – 4.95 (m, 2H), 4.93 (dd, 1H), 4.71 (dd, 1H), 4.61 (dt, 2H), 3.97 – 3.90 (m, 2H), 3.68 (dd, 1H), 3.62 (dd, 1H), 2.41 (t, 2H), 1.81 – 1.71 (m, 2H), 1.70 – 1.60 (m, 2H), 1.16 (s, 9H).

Alternatively, Compound (1) can be prepared by the following synthesis:

- 25 **Step 1':** Synthesis of (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 2,2-dimethyl propanoate (corresponding to compound (1c), wherein R is selected from formula (II))

In a three necked 500 ml round bottom flask, 1,4:3,6-dianhydro-D-mannitol (14.2 g,

97.4 mmol) was suspended in dry DCM (150 ml) under stirring. DMAP (2.98 g, 24.3 mmol) was then added and the mixture was stirred for 10 minutes to obtain complete dissolution.

A solution of trimethylacetyl chloride (2.94g, 24.3 mmol) in DCM (25 ml) was added dropwise in approx. 30 minutes. The reaction was left under stirring at rt overnight.

5 The organic phase was washed with water (2x150 ml), dried over MgSO₄ and the solvent removed under vacuum.

The obtained oil was purified on a 340g silica cartridge using Cyclohexane/EtOAc (from 6/4 to 4/6) as eluent. The fractions containing clean product were pooled together and the solvent was removed under vacuum to give 5.4 g (24% yield) of the desired product
10 as a clear oil.

MS ESI+: 231[M+H⁺]; 235[M+Na⁺]

Purity > 90%@210nm

Step 2': Synthesis of (S)-((3R,3aR,6R,6aR)-6-(pivaloyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate ((S)-isomer of Compound (2)).

15 In a three necked 250 ml round bottom flask, (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 2,2-dimethyl propanoate (2.4g, 10.4 mmol) (obtained in Example 1, Step 1') was dissolved in dry DCM (90ml). DCC (2.58 g, 12.5 mmol) and DMAP (1.27g, 10.4 mmol) were added and finally (5S)-5,6-bis(nitrooxy)hexanoic acid (obtained in Example 1, Step 5) (2.98g, 12.5 mmol) was added.
20 The mixture was left at rt under stirring overnight.

The organic phase was filtered on a celite pad and then washed with water (2x100 ml), dried over MgSO₄ and the solvent removed under vacuum (water bath 30°C max).

The obtained crude was purified on a 240 g silica cartridge using Cyclohexane/EtOAc (from 8/2 to 7/3) as eluent. The fractions containing clean product
25 were pooled together and the solvent was removed under vacuum (water bath 30°C max) to give 3.8 g (81% yield) of the desired product as a light yellow oil.

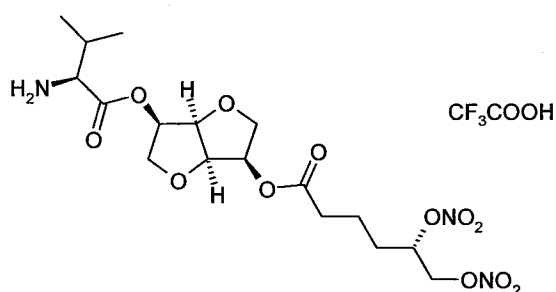
MS ESI+: 451[M+H⁺]; 473[M+Na⁺]

Purity > 98%@210 nm

¹H NMR (600 MHz, DMSO-d₆) δ 5.46 – 5.40 (m, 1H), 5.01 – 4.95 (m, 2H), 4.93 (dd, 1H), 4.71 (dd, 1H), 4.61 (dt, 2H), 3.97 – 3.90 (m, 2H), 3.68 (dd, 1H), 3.62 (dd, 1H), 2.41 (t, 2H), 1.81 – 1.71 (m, 2H), 1.70 – 1.60 (m, 2H), 1.16 (s, 9H).

Example 2

5 Synthesis of (S)-((3R,3aR,6R,6aR)-6-((S)-2-amino-3-methylbutanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate trifluoroacetic acid salt ((S)-isomer of compound (6)-trifluoroacetic acid salt)



10 (6)

Step 1: Synthesis of (S)-((3R,3aR,6R,6aR)-6-((S)-2-(tert-butoxycarbonylamino)-3-methylbutanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate.

To a solution of (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (200 mg, 0.55 mmol), DCC (113 mg, 0.55 mmol) and DMAP (67 mg, 0.55 mmol) in dry DCM (4 ml), Boc-L-valine (143 mg, 0.66 mmol) was added.

The mixture was stirred 2-3 hours at room temperature, checking the conversion by LC-MS. Once the conversion was complete, the precipitate was filtered off and the solution washed with water. The two phases were separated and the aqueous phase extracted twice with DCM. The combined organic phases were dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (isocratic elution cyclohexane/ethyl acetate 75:25), affording the title compound (0.247 mg, 80%).

Step 2: Synthesis of (S)-((3R,3aR,6R,6aR)-6-((S)-2-amino-3-methylbutanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate trifluoro acetic acid salt ((S)-isomer of compound (6)-trifluoroacetic salt).

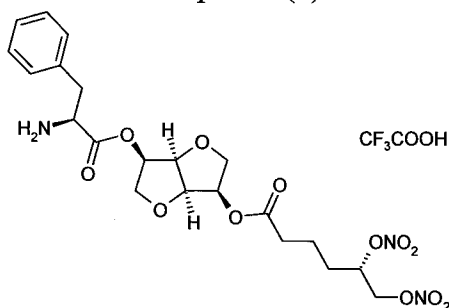
25 To a solution of (S)-((3R,3aR,6R,6aR)-6-((S)-2-(tert-butoxycarbonylamino)-3-

methylbutanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (0.44 mmol) in dry DCM (1.5 ml), trifluoroacetic acid (4.4 mmol) was added. The mixture was stirred 2 hours at room temperature. Then, the mixture was diluted with DCM and a saturated Na₂CO₃ solution was added. The two phases were separated and the aqueous phase extracted twice with DCM. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by reversed-phase chromatography (isocratic elution water/acetonitrile 8:2 with 0.01% TFA v/v), affording 0.23 g the desired product (yield 74%).

¹H NMR (600 MHz, DMSO-d₆) δ 7.15 (bs, 3H), 5.42 (m, 1H), 5.12 (q, J = 6.0 Hz, 1H), 5.02 (q, J = 6.2 Hz, 1H), 4.93 (dd, J = 12.9, 2.6 Hz, 1H), 4.71 (dd, J = 12.9, 5.9 Hz, 1H), 4.67 (t, J = 5.3 Hz, 1H), 4.63 (t, J = 5.3 Hz, 1H), 3.99 – 3.92 (m, 2H), 3.78 (d, J = 4.6 Hz, 1H), 3.72 – 3.66 (m, 2H), 2.46 – 2.35 (m, 2H), 2.15 – 2.04 (m, 1H), 1.80 – 1.71 (m, 2H), 1.68 – 1.60 (m, 2H), 0.95 (d, 6H).

Example 3

Synthesis of (S)-((3R,3aR,6R,6aR)-6-((S)-2-amino-3-phenylpropanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate trifluoroacetic acid salt ((S)-isomer of compound (9)-trifluoroacetic acid salt)



(9)

Step 1: Synthesis of (S)-((3R,3aR,6R,6aR)-6-((S)-2-(tert-butoxycarbonylamino)-3-phenylpropanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate.

Starting from (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Example 1, Step 8) (0.55 mmol) and Boc-L-phenylalanine (0.66 mmol), following the procedure described in Example 2, Step 1, the title compound

was obtained (236.23 mg, 70% yield)

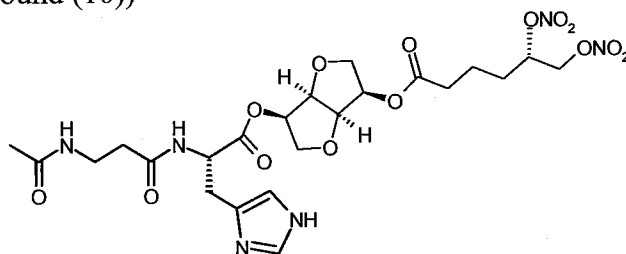
Step 2: Synthesis of (S)-((3R,3aR,6R,6aR)-6-((S)-2-amino-3-phenylpropanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate, trifluoroacetic acid salt ((S)-isomer of compound (9)-trifluoroacetic acid salt).

Starting from (S)-((3R,3aR,6R,6aR)-6-((S)-2-(tert-butoxycarbonylamino)-3-phenylpropanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate and following the procedure described in Example 2, Step 2, the title compound was obtained (236.23 mg, 70% yield)

¹H NMR (600 MHz, DMSO-d₆) δ 8.46 (s, 3H), 7.57 – 6.97 (m, 5H), 5.05 (m, 1H), 4.98 (m, 1H), 4.93 (dd, J = 12.9, 2.6 Hz, 1H), 4.71 (dd, J = 12.9, 5.9 Hz, 1H), 4.64 (t, J = 5.3 Hz, 1H), 4.59 (t, J = 5.3 Hz, 1H), 4.38 (t, J = 6.9 Hz, 1H), 3.92 (dd, J = 9.2, 6.4 Hz, 1H), 3.80 (dd, J = 9.5, 6.1 Hz, 1H), 3.57 (dd, J = 9.2, 6.9 Hz, 1H), 3.47 (dd, J = 9.5, 6.1 Hz, 1H), 3.16 (dd, J = 14.1, 6.0 Hz, 1H), 3.05 (dd, J = 14.1, 7.6 Hz, 1H), 2.47 – 2.29 (m, 2H), 1.80-1.70 (m, 2H), 1.69-1.58 (m, 2H).

Example 4

Synthesis of (S)-((3R,3aR,6R,6aR)-6-((S)-2-(3-acetamidopropanamido)-3-(1H-imidazol-4-yl)propanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate ((S)-isomer of compound (10))



(10)

To a solution of (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Example 1, Step 8) (150 mg, 0.410 mmol), DCC (84 mg, 0.410 mmol) and DMAP (28 mg, 0.229 mmol) in dry DMF (3 ml), N-acetyl-L-carnosine (132 mg, 0.491 mmol) was added.

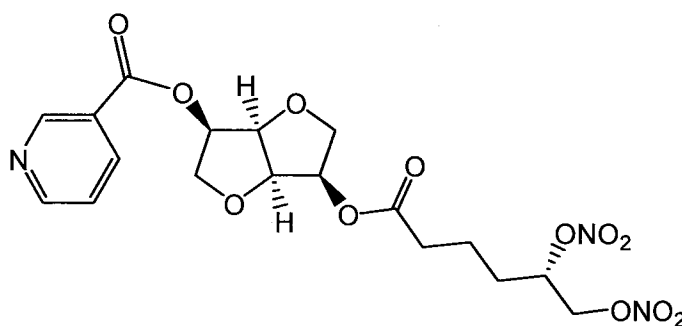
The mixture was stirred overnight at room temperature. After 18h other 0.410 mmol

(84 mg) of DCC and 0.491 mmol (132 mg) of N-acetyl-L-carnosine were added, and the mixture was stirred 3 days at room temperature. The precipitate was filtered off and the solution washed with water. The two phases were separated and the aqueous phase extracted twice with DCM. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (methanol in ethyl acetate from 5% to 50% in 12 CV), affording 51 mg of the desired product (yield: 20%).

¹H NMR (600 MHz, DMSO-d₆) δ 8.18 (d, 1H), 7.87 – 7.79 (m, 1H), 7.53 (s, 1H), 6.88 – 6.78 (m, 1H), 5.05 – 4.87 (m, 1H), 3.97 – 3.82 (m, 1H), 3.50 – 3.40 (m, 1H), 3.25 – 3.10 (m, 2H), 3.08 – 2.67 (m, 2H), 2.45 – 2.36 (m, 1H), 2.30 – 2.16 (m, 2H), 1.87 – 0.95 (m, 18H).

Example 5

Synthesis of (3R,3aR,6R,6aR)-6-((S)-5,6-bis(nitrooxy)hexanoyloxy)hexahydrofuro[3,2-b]furan-3-yl nicotinate ((S)-isomer of compound (12))



(12)

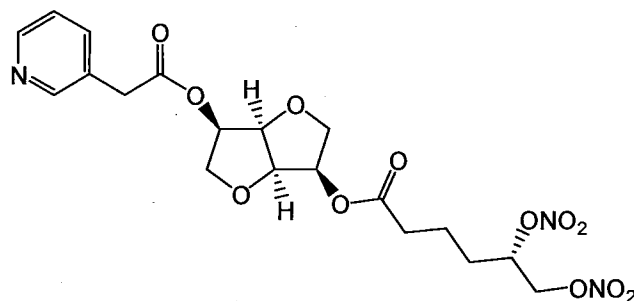
To a solution of (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Example 1, Step 8) (100 mg, 0.273 mmol) in dry DCM (3 ml), triethylamine (0.17 ml, 1.229 mmol) and nicotinoyl chloride hydrochloride (73 mg, 0.410 mmol) were added. The mixture was stirred overnight at room temperature, then diluted with DCM and water. The two phases were separated and the aqueous phase extracted twice with DCM. The combined organic phases were dried over MgSO₄ and

concentrated under reduced pressure. The residue was purified by reversed-phase chromatography (H₂O/CH₃CN with 0.01% TFA, from 80:20 to 40:60). DCM and a saturated solution of NaHCO₃ were added to the residue after purification. The two phases were separated and the aqueous phase extracted twice with DCM. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. The obtained residue was further purified by flash chromatography (cyclohexane/ethyl acetate from 50:50 to 20:80), to give 71 mg of the desired product (yield: 55.2%).

¹H NMR (400 MHz, DMSO-d₆) δ 9.12 (dd, 1H), 8.84 (dd, 1H), 8.34 – 8.29 (m, 1H), 7.60 (dq, 1H), 5.47 – 5.40 (m, 1H), 5.31 (q, 1H), 5.03 (q, 1H), 4.93 (dd, 1H), 4.78 (t, 1H), 4.75 – 4.65 (m, 2H), 4.05 (dd, 1H), 3.97 – 3.87 (m, 2H), 3.68 (dd, 1H), 2.43 (t, 2H), 1.82 – 1.61 (m, 4H).

Example 6

Synthesis of (S)-((3R,3aR,6R,6aR)-6-(2-(pyridin-3-yl)acetoxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate ((S)-isomer of compound (13))



(13)

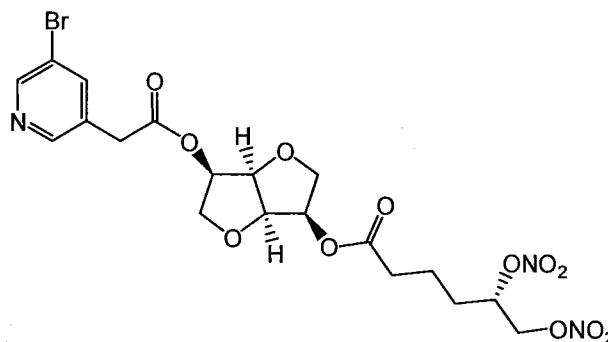
To a solution of (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Example 1, Step 8) (100 mg, 0.273 mmol) in dry DCM (3 ml), DMAP (73 mg, 0.601 mmol), DCC (112 mg, 0.546 mmol) and 3-pyridylacetic acid hydrochloride (57 mg, 0.328 mmol) were added. The mixture was stirred overnight at room temperature, then DMAP (73 mg, 0.601 mmol) and 3-pyridylacetic acid hydrochloride (57 mg, 0.328 mmol) were added. The mixture was allowed to stir for 4 hours. The solid was filtered off, water and DCM were added, the two phases were separated and the aqueous phase extracted twice with DCM. The combined organic phases were dried over

MgSO₄ and concentrated under reduced pressure. The residue was purified by reversed-phase chromatography (H₂O/CH₃CN from 95:5 to 30:70), to give 58 mg of the desired product (yield: 43.8%).

¹H NMR (600 MHz, DMSO-*d*₆) δ 8.49 – 8.46 (m, 2H), 7.72 – 7.68 (m, 1H), 7.38 – 7.34 (m, 1H), 5.45 – 5.40 (m, 1H), 5.05 (q, 1H), 4.97 (q, 1H), 4.93 (dd, 1H), 4.71 (dd, 1H), 4.64 – 4.58 (m, 2H), 3.92 (dd, 1H), 3.87 (dd, 1H), 3.79 (s, 2H), 3.68 (dd, 1H), 3.56 (dd, 1H), 2.41 (t, 2H), 1.80 – 1.72 (m, 2H), 1.68 – 1.60 (m, 2H).

Example 7

Synthesis of (S)-((3R,3aR,6R,6aR)-6-(2-(5-bromopyridin-3-yl)acetoxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate ((S)-isomer of compound (14))



(14)

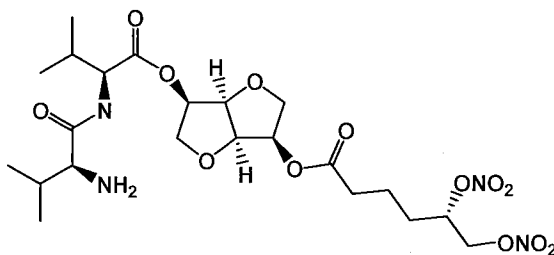
To a solution of (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Example 1, Step 8) (100 mg, 0.273 mmol) in dry DCM (3 ml), DMAP (34 mg, 0.273 mmol), DCC (62 mg, 0.300 mmol) and 5-bromo-3-pyridylacetic acid (65 mg, 0.300 mmol) were added. The mixture was stirred overnight at room temperature, then concentrated under reduced pressure. The residue was purified by reversed-phase chromatography (H₂O/CH₃CN from 90:10 to 20:80), to give 106 mg of the desired product (yield: 68.8%).

¹H NMR (600 MHz, DMSO-*d*₆) δ 8.62 (d, 1H), 8.49 (d, 1H), 8.02 – 8.00 (m, 1H), 5.45 – 5.40 (m, 1H), 5.06 (q, 1H), 4.98 (q, 1H), 4.93 (dd, 1H), 4.71 (dd, 1H), 4.64 – 4.58 (m, 2H), 3.93 (dd, 1H), 3.88 (dd, 1H), 3.84 (s, 2H), 3.69 (dd, 1H), 3.56 (dd, 1H), 2.41 (t, 2H), 1.79 – 1.72 (m, 2H), 1.69 – 1.60 (m, 2H).

Example 8

Synthesis of (S)-((3R,3aR,6R,6aR)-6-((S)-2-((S)-2-amino-3-methylbutanamido)-3-methylbutanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate ((S)-isomer of compound (15) -trifluoroacetic acid salt)

5



Step 1: synthesis of (3R,3aR,6R,6aR)-6-(((tert-butoxycarbonyl)-L-valyl)oxy)hexahydrofuro[3,2-b]furan-3-yl (S)-5,6-bis(nitrooxy)hexanoate

To a solution of (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Example 1, Step 8) (300 mg, 0.819 mmol), DCC (170 mg, 0.819 mmol) and DMAP (100 mg, 0.819 mmol) in dry DCM (4 ml), *N*-Boc-L-valine (213 mg, 0.982 mmol) was added.

The mixture was stirred for 1 hour at room temperature. The solid was filtered off, water and DCM were added, the two phases were separated and the aqueous phase extracted twice with DCM. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by reversed-phase chromatography (H₂O/CH₃CN), to give 343mg of (3R,3aR,6R,6aR)-6-(((tert-butoxycarbonyl)-L-valyl)oxy)hexahydrofuro[3,2-b]furan-3-yl (S)-5,6-bis(nitrooxy)hexanoate (yield: 74%).

Step 2: synthesis of (S)-1-(((3R,3aR,6R,6aR)-6-(((S)-5,6-bis(nitrooxy)hexanoyl)oxy)hexahydrofuro[3,2-b]furan-3-yl)oxy)-3-methyl-1-oxobutan-2-aminium trifluoroacetate

To a solution of (3R,3aR,6R,6aR)-6-(((tert-butoxycarbonyl)-L-valyl)oxy)hexahydrofuro[3,2-b]furan-3-yl (S)-5,6-bis(nitrooxy)hexanoate (334 mg, 0.591 mmol) in dry DCM (1.5 ml), trifluoroacetic acid (0.46 ml, 5.90 mmol) was added. The mixture was stirred 1 hour at room temperature, then it was concentrated and dried

under reduced pressure, to give 336 mg of (S)-1-(((3R,3aR,6R,6aR)-6-(((S)-5,6-bis(nitrooxy)hexanoyl)oxy) hexahydrofuro[3,2-b]furan-3-yl)oxy)-3-methyl-1-oxobutan-2-aminium trifluoroacetate (crude yield: 98%), which was used in the following step without further purification.

5 **Step 3:** synthesis of (3R,3aR,6R,6aR)-6-(((S)-2-(((tert-butoxycarbonyl)-L-valyl)oxy)-3-methylbutanoyl)oxy)hexahydrofuro[3,2-b]furan-3-yl (S)-5,6-bis(nitrooxy)hexanoate

To a solution of (S)-1-(((3R,3aR,6R,6aR)-6-(((S)-5,6-bis(nitrooxy)hexanoyl)oxy) hexahydrofuro[3,2-b]furan-3-yl)oxy)-3-methyl-1-oxobutan-2-aminium trifluoroacetate
10 (336 mg, 0.580 mmol) in dry DCM (4 ml) at 0 °C, DCC (120 mg, 0.580 mmol), DMAP (71 mg, 0.580 mmol) and TEA (0.12 ml, 0.870 mmol) were added. *N*-Boc-L-valine (151 mg, 0.696 mmol) was added, then the mixture was allowed to reach room temperature and stirred for 1 hour. The solid was filtered off, water and DCM were added to the mixture, the two phases were separated and the aqueous phase extracted twice with DCM. The
15 combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by reversed-phase chromatography (H₂O/CH₃CN), to give
310 mg of (3R,3aR,6R,6aR)-6-(((S)-2-(((tert-butoxycarbonyl)-L-valyl)oxy)-3-methylbutanoyl)oxy)hexahydrofuro[3,2-b]furan-3-yl-(S)-5,6-bis(nitrooxy)hexanoate
(yield 80%).

20 **Step 4:** synthesis of 1-((1-(((3R,3aR,6R,6aR)-6-(((S)-5,6-bis(nitrooxy)hexanoyl)oxy) hexahydrofuro[3,2-b]furan-3-yl)oxy)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-aminium trifluoroacetate

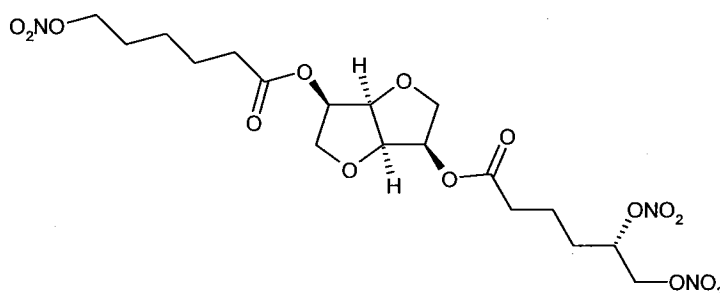
To a solution of (3R,3aR,6R,6aR)-6-(((S)-2-(((tert-butoxycarbonyl)-L-valyl)oxy)-3-methylbutanoyl)oxy)hexahydrofuro[3,2-b]furan-3-yl (S)-5,6-bis(nitrooxy)hexanoate
25 (310 mg, 0.466 mmol) in dry DCM (1.5 ml), trifluoroacetic acid (0.36 ml, 4.66 mmol) was added. The mixture was stirred 1 hour at room temperature, then it was concentrated and dried under reduced pressure, to give 313 mg of the desired product (yield: 99%) as a colourless oil.

¹H NMR (600 MHz, DMSO-d₆) δ 8.58 (d, 1H), 8.11 – 8.05 (m, 2H), 5.45 – 5.39 (m, 1H), 5.04 (q, 1H), 5.00 (q, 1H), 4.93 (dd, 1H), 4.71 (dd, 1H), 4.64 – 4.59 (m, 2H), 4.28 (dd, 1H), 3.93 – 3.89 (m, 2H), 3.74 – 3.59 (m, 4H), 2.42 – 2.38 (t, 2H), 2.14 – 2.04 (m, 2H), 1.79 – 1.61 (m, 4H), 0.97 – 0.91 (m, 12H).

5 **Example 9 (Comparative example)**

Intraocular pressure (IOP) lowering activity in ocular normotensive New Zealand White (NZW) rabbits

The intraocular pressure (IOP) lowering activities of compound (2)/(S)-isomer and reference compound (RF) (S)-((3R,3aR,6R,6aR)-6-(6-(nitrooxy)hexanoyloxy) hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate reported below were assessed in ocular normotensive rabbits.



(RF)

15 Reference compound is a compound included in the prior art document EP 2 238 143;

Compound (2)/(S)-isomer is disclosed in Example 1 of the present invention.

Procedure

Adult male NZW rabbits weighting 1.8-2.0 Kg were used in the experiments.

20 IOP was measured using a pneumatonometer 30 CLASSICTM before topical application (basal) and at different time points (30, 60, 180, 240 and 300 min) thereafter. Eyes were randomly assigned to different treatment groups.

Compound (2)/(S)-isomer 1% w/v, RF 1% w/v or vehicle (cremophor-EL 5% w/v, DMSO 0.3% w/v, Benzalkonium chloride (BAC) 0.2 mg/ml in PBS pH 6.0) were topically

administered as eye drops into the conjunctiva pocket.

One drop of 0.4% oxybuprocaine hydrochloride (Novesine, Sandoz) was instilled in each eye immediately before each set of ocular pressure measurements.

The ocular hypotensive activities of compound (2)/(S)-isomer and of reference compound are reported in Table 1 and expressed as IOP change versus vehicle and versus IOP at basal (mean $\pm$ standard error).

In Table 1 the data related to the IOP reducing effects of isosorbide mononitrate (ISMN) (1% w/v) are reported; the hypotensive effects of ISMN were evaluated in the same model of ocular normotensive rabbit in the same laboratory in a different group of rabbits.

Isosorbide mononitrate is a known nitric oxide donating compound.

Despite the Reference compound has three nitric oxide releasing groups i.e. -ONO₂ groups, in this comparative efficacy study compound (2)/(S)-isomer of the invention was found to be more effective and showed a longer duration of intraocular pressure lowering action effects.

Landmark glaucoma studies highlighted that every mm Hg IOP lowering is associated with a 10-19% decrease in risk of progression of glaucomatous visual field loss (Anders Heijl, The Lancet 2015; 385: 1264-1266).

Table 1: Intraocular pressure (IOP) lowering activity in ocular normotensive NZW rabbits					
	30 min.	60 min.	180 min.	240 min.	300 min.
Compound (2)/ (S)-isomer	-3.0 $\pm$ 0.6	-3.6 $\pm$ 0.8	-2.0 $\pm$ 0.9	-1.2 $\pm$ 0.8	-0.1 $\pm$ 0.5
Ref. Compound	-1.9 $\pm$ 0.4	-1.2 $\pm$ 0.4	-0.9 $\pm$ 0.7	-0.8 $\pm$ 0.5	-0.0 $\pm$ 0.6
ISMN	-1.5 $\pm$ 0.3	-1.7 $\pm$ 0.4	-0.5 $\pm$ 0.3	-0.8 $\pm$ 0.4	-0.8 $\pm$ 0.4

Example 10

Intraocular pressure (IOP) lowering activity in ocular normotensive New Zealand White (NZW) rabbits

The Intraocular pressure (IOP) lowering activities of compound (13)/(S)-isomer and

compound (15)/(S)-isomer of the invention were assessed in ocular normotensive rabbits.

Compounds (13)/(S)-isomer and (15)/(S)-isomer are disclosed in Examples 6 and 8 respectively of the present invention.

Procedure

5 Adult male NZW rabbits weighting 1.8-2.0 Kg were used in the experiments.

IOP was measured using a pneumatonometer 30 CLASSICTM before topical application (basal) and at different time points (60, 120 and 240) thereafter. Eyes were randomly assigned to different treatment groups.

10 Compound (13)/(S)-isomer 27.3 mM (1.3% w/v), compound (15)/(S)-isomer 27.3 nM (1.54% w/v) or vehicle (cremophor-EL 5% w/v, DMSO 0.3% w/v, BAC 0.2 mg/ml in PBS pH 6.0) were topically administered as eye drops into the conjunctiva pocket.

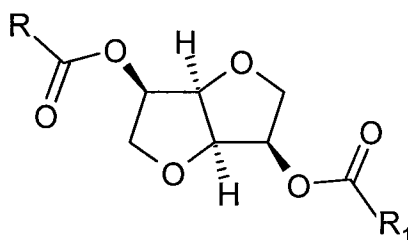
One drop of 0.4% oxybuprocaine hydrochloride (Novesine, Sandoz) was instilled in each eye immediately before each set of ocular pressure measurements.

15 The ocular hypotensive activities of compounds (13) and (15) are reported in Table 2 and they are expressed as IOP change versus vehicle and versus IOP at basal (mean $\pm$ standard error).

Table 2: Intraocular pressure (IOP) lowering activity in ocular normotensive NZW rabbits			
	60 min.	120 min.	240 min.
Compound (13)/(S)-isomer	-2.7 $\pm$ 0.8	-1.1 $\pm$ 0.8	-1.1 $\pm$ 0.7
Compound (15)/(S)-isomer	-3.2 $\pm$ 0.6	-1.1 $\pm$ 0.4	-1.0 $\pm$ 0.5

CLAIMS

1 A compound of formula (I)



(I)

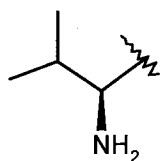
or a pharmaceutical acceptable salt or stereoisomers thereof

wherein:

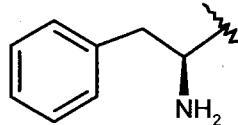
R is selected from the following structures:



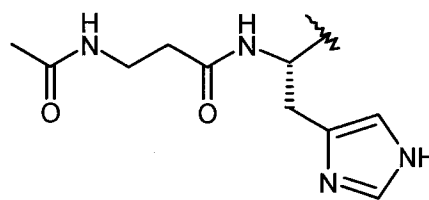
(II)



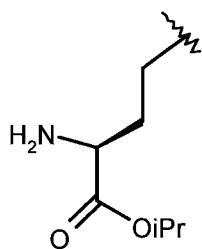
(III)



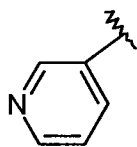
(IV)



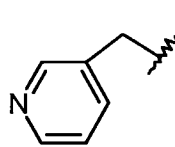
(V)



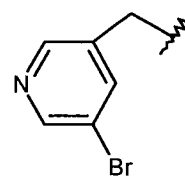
(VI)



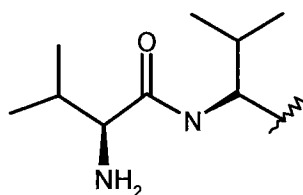
(VII)



(VIII)



(IX)



(X)

R₁ is -(CH₂)_m-[O-(CH₂)_n]_p-(CH-ONO₂)_q-CH₂-ONO₂

wherein

p is 1 or 0;

q is 1 or 0;

m is an integer ranging from 1 to 10; preferably 1 to 6;

n is an integer ranging from 1 to 6; preferably 1 or 2.

2. A compound according to claim 1 wherein:

5 R_1 is $-(CH_2)_m-[O-(CH_2)_n]_p-(CH-ONO_2)_q-CH_2-ONO_2$

p is 0;

q is 0;

and m is an integer ranging from 1 to 6.

3. A compound according to claim 1 wherein:

10 R_1 is $-(CH_2)_m-[O-(CH_2)_n]_p-(CH-ONO_2)_q-CH_2-ONO_2$

p is 0;

q is 1;

m is an integer ranging from 1 to 6.

4. A compound according to claim 1 wherein:

15 R_1 is $-(CH_2)_m-[O-(CH_2)_n]_p-(CH-ONO_2)_q-CH_2-ONO_2$

p is 1;

q is 0 or 1;

m is an integer ranging from 1 to 6;

n is 1 or 2.

20 5. A compound according to claim 1 wherein R_1 are selected from the following structures:

(a) $-(CH_2)_3-(CH-ONO_2)-CH_2-ONO_2$,

(b) $-(CH_2)_4-CH_2-ONO_2$,

(c) $-(CH_2)-O-(CH_2)-CH_2-ONO_2$ or

25 (d) $-(CH_2)_2-O-(CH_2)-(CH-ONO_2)-CH_2-ONO_2$.

6. A compound according to claim 1 wherein:

R is

41



(II)

7. A compound according to claim 6 wherein:

R_1 is $-(CH_2)_m-[O-(CH_2)_n]_p-(CH-ONO_2)_q-CH_2-ONO_2$

p is 0;

5 q is 0;

and m is an integer ranging from 1 to 6.

8. A compound according to claim 6 wherein:

R_1 is $-(CH_2)_m-[O-(CH_2)_n]_p-(CH-ONO_2)_q-CH_2-ONO_2$

p is 0;

10 q is 1;

m is an integer ranging from 1 to 6.

9. A compound according to claim 6 wherein:

R_1 is $-(CH_2)_m-[O-(CH_2)_n]_p-(CH-ONO_2)_q-CH_2-ONO_2$

p is 1;

15 q is 0 or 1;

m is from 1 to 6;

n is 1 or 2.

10. A compound according to claim 6 wherein R_1 are selected from the following structures:

20 (a) $-(CH_2)_3-(CH-ONO_2)-CH_2-ONO_2$,

(b) $-(CH_2)_4-CH_2-ONO_2$,

(c) $-(CH_2)-O-(CH_2)-CH_2-ONO_2$ or

(d) $-(CH_2)_2-O-(CH_2)-(CH-ONO_2)-CH_2-ONO_2$.

11. A compound according to claim 1 selected from the following group:

25 (3R,3aR,6R,6aR)-6-(pivaloyloxy)hexahydrofuro[3,2-b]furan-3-yl-6-(nitrooxy)hexanoate
(Compound (1));

- (3R,3aR,6R,6aR)-6-(pivaloyloxy)hexahydrofuro[3,2-b]furan-3-yl-5,6-bis(nitrooxy)hexanoate (Compound (2));
- (3R,3aR,6R,6aR)-6-(2-(2-(nitrooxy)ethoxy)acetoxy)hexahydrofuro[3,2-b]furan-3-yl-pivalate (Compound (3));
- 5 (3R,3aR,6R,6aR)-6-(3-(2,3-bis(nitrooxy)propoxy)propanoyloxy)hexahydrofuro[3,2-b]furan-3-yl-pivalate (Compound (4));
- (3R,3aR,6R,6aR)-6-((S)-2-amino-3-methylbutanoyloxy)hexahydrofuro[3,2-b]furan-3-yl-6-(nitrooxy)hexanoate (Compound (5));
- (3R,3aR,6R,6aR)-6-((S)-2-amino-3-methylbutanoyloxy)hexahydrofuro[3,2-b]furan-3-yl-5,6-bis(nitrooxy)hexanoate (Compound (6));
- 10 (S)-((3R,3aR,6R,6aR)-6-(2-(2-(nitrooxy)ethoxy)acetoxy)hexahydrofuro[3,2-b]furan-3-yl)-2-amino-3-methylbutanoate (Compound (7));
- (2S)-((3R,3aR,6R,6aR)-6-(3-(2,3-bis(nitrooxy)propoxy)propanoyloxy)hexahydrofuro[3,2-b]furan-3-yl)-2-amino-3-methylbutanoate (Compound (8));
- 15 (3R,3aR,6R,6aR)-6-((S)-2-amino-3-phenylpropanoyloxy)hexahydrofuro[3,2-b]furan-3-yl-5,6-bis(nitrooxy)hexanoate (Compound (9));
- (3R,3aR,6R,6aR)-6-((S)-2-(3-acetamidopropanamido)-3-(1H-imidazol-5-yl)propanoyloxy)hexahydrofuro[3,2-b]furan-3-yl-5,6-bis(nitrooxy)hexanoate (Compound (10));
- 20 (2S)-5-((3R,3aR,6R,6aR)-6-(5,6-bis(nitrooxy)hexanoyloxy)hexahydrofuro[3,2-b]furan-3-yl)-1-isopropyl-2-aminopentanedioate (Compound (11));
- (3R,3aR,6R,6aR)-6-(5,6-bis(nitrooxy)hexanoyloxy)hexahydrofuro[3,2-b]furan-3-yl-nicotinate (Compound (12));
- 25 (3R,3aR,6R,6aR)-6-(2-(pyridin-3-yl)acetoxy)hexahydrofuro[3,2-b]furan-3-yl-5,6-bis(nitrooxy)hexanoate (Compound (13));
- (3R,3aR,6R,6aR)-6-(2-(5-bromopyridin-3-yl)acetoxy)hexahydrofuro[3,2-b]furan-3-yl-5,6-bis(nitrooxy)hexanoate (Compound (14));

(3R,3aR,6R,6aR)-6-((S)-2-((S)-2-amino-3-methylbutanamido)-3-methylbutanoyloxy)hexahydrofuro[3,2-b]furan-3-yl 5,6-bis(nitrooxy)hexanoate (Compound (15)).

12. A compound according to claim 1 selected from the following group:

- (S)-((3R,3aR,6R,6aR)-6-(pivaloyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Compound (2) (S)-isomer);
- (S)-((3R,3aR,6R,6aR)-6-((S)-2-amino-3-methylbutanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate trifluoroacetic acid salt (compound (6) (S)-isomer);
- (S)-((3R,3aR,6R,6aR)-6-((S)-2-amino-3-phenylpropanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate trifluoroacetic acid salt (compound (9) (S)-isomer);
- (S)-((3R,3aR,6R,6aR)-6-((S)-2-(3-acetamidopropanamido)-3-(1H-imidazol-4-yl)propanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Compound (10) (S)-isomer);
- (3R,3aR,6R,6aR)-6-((S)-5,6-bis(nitrooxy)hexanoyloxy)hexahydrofuro[3,2-b]furan-3-yl nicotinate (Compound (12) (S)-isomer);
- (S)-((3R,3aR,6R,6aR)-6-(2-(pyridin-3-yl)acetoxo)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Compound (13) (S)-isomer);
- (S)-((3R,3aR,6R,6aR)-6-(2-(5-bromopyridin-3-yl)acetoxo)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Compound (14) (S)-isomer);
- (S)-((3R,3aR,6R,6aR)-6-((S)-2-((S)-2-amino-3-methylbutanamido)-3-methylbutanoyloxy)hexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Compound (15) (S)-isomer).

13. A compound of formula (I) according to any of claims 1 to 12 for use as medicament.

14. A compound of formula (I) according to any of claims 1 to 12 for use in the treatment of glaucoma or ocular hypertension.

15. A compound of formula (I) for the use according to claim 14, wherein glaucoma is primary open angle glaucoma, normal intraocular tension glaucoma, pseudoexfoliation glaucoma, acute angle-closure glaucoma or chronic closed angle glaucoma.

16. A compound of formula (I) for the use according to claims 14 or 15 wherein the compound of formula (I) is simultaneously, separately or sequentially administered with another active agent selected from the following classes of drugs: prostaglandin analogues, beta-adrenergic antagonists carbonic anhydrase inhibitors, cholinergic agonists, steroids or cholinesterase inhibitors.
17. A topical ocular pharmaceutical composition comprising a compound of formula (I) according to any of claims 1 to 12 as active principle and pharmaceutically acceptable excipients.
18. A topical ocular composition according to claim 17 further comprising at least another active agent selected from the following classes of drugs: beta-adrenergic antagonists, prostaglandin analogs, adrenergic agonists, carbonic anhydrase inhibitors, cholinergic agonists or cholinesterase inhibitors.
19. The composition of claim 18 which is a kit comprising a topical ocular dosage form comprising a compound of formula (I) and another topical ocular dosage form comprising an active agent selected from the following classes of drugs: prostaglandin analogues, beta-adrenergic antagonists, carbonic anhydrase inhibitors, cholinergic agonists, steroids or cholinesterase inhibitors.
20. A composition according to claims 18 or 19 for use in the treatment of glaucoma or ocular hypertension.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/064568

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D493/04 A61K31/34 A61P27/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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