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(54) Title: COMBINATIONS OF PROSTAGLANDINS AND NITRIC OXIDE DONORS

(57) Abstract: The present invention relates to compositions for treating glaucoma and elevated ocular pressure. The compositions comprise a nitric oxide releasing isomannide derivative and a prostaglandin $F_{2\alpha}$ analog.

COMBINATIONS OF PROSTAGLANDINS AND NITRIC OXIDE DONORS

The present invention relates to compositions comprising a Nitric oxide releasing isomannide derivative and a prostaglandin $F_{2\alpha}$ analog. More specifically, the invention discloses compositions for lowering intraocular pressure associated with glaucoma or with other ocular diseases.

Glaucoma, including hypertensive and normotensive glaucoma, is a disease of the eye characterized by a progressive loss of visual field due to irreversible damage to the optic nerve to the point where, if inadequately treated, glaucoma can lead to blindness or significant loss of vision.

Prior art treatment of glaucoma consists in lowering the intraocular pressure by administering drugs which either reduce the production of aqueous humor within the eye or increase the fluid drainage, such as beta adrenergic blockers, α-agonists, cholinergic agents, carbonic anhydrase inhibitors, and prostaglandin analogs.

Of these drugs, prostaglandin analogs facilitate aqueous humor from the uveoscleral outflow, thereby lowering intraocular pressure, and thus are commonly used in the treatment of glaucoma. However prostaglandin analogs such as, for example, bimatoprost, latanoprost, travoprost, tafluprost and unoprostone isopropyl, can produce ocular side effects, such as ocular irritation, conjunctival hyperaemia, iritis, uveitis, macular oedema, and increased pigmentation of the iris at therapeutically effective doses (Martindale, Thirty-third edition, p. 1445).

In the treatment of glaucoma and ocular hypertension, drugs having an intraocular pressure lowering action are used in combination to enhance the intraocular pressure lowering action. For example, EP 0 286 903 discloses the use of combinations of prostaglandin and a beta-adrenergic blocking agent US2013/0116254 discloses combination of the intraocular-lowering agents bimatoprost, brimonidine, and timolol.

Furthermore, WO 2013/060673, WO2014/170264 and WO2014/063923

disclose the use of quinone based nitric oxide donors alone and in combinations with prostaglandin analogs for treating glaucoma and intraocular pressure. The quinone based nitric oxide donors are disclosed for ophthalmic use. However, the patent applications do not provide evidence concerning the effects brought about by combining the quinone based nitric oxide donors with prostaglandin analogs.

EP 2 238 143B discloses nitric oxide releasing isohexide derivatives. The compounds have been disclosed for their use for treating cardiovascular diseases, hypertension, inflammation, pain, respiratory diseases, vascular diseases nephropathies and other pathological conditions including glaucoma and ocular hypertension. However, the patent does not provide evidence concerning the effects of the combination of a nitric oxide releasing isohexide derivatives and a prostaglandin analog.

US 7,816,399 discloses the use of a mixture of latanoprost and a nitric oxide (NO) donor for treating or preventing ocular hypertension or glaucoma.

The patent discloses that combinations of latanoprost with nipradilol or sodium nitroprusside increase the ocular tension reducing effect when compared to the compounds used individually.

It has been unexpectedly found that the administration of nitric oxide releasing isomannide derivatives and prostaglandin $F_{2\alpha}$ analogs in combination exerts a greater reduction of intraocular pressure and a longer intraocular pressure decrease with respect to the same dose of either one of the two compounds given separately.

The synergic effect on the reduction of the intraocular pressure following co-administration of the nitric oxide releasing isomannide derivative and the prostaglandin $F_{2\alpha}$ analog will allow reducing the dosage of the prostaglandin $F_{2\alpha}$ analog thus decreasing or eliminating the side effects normally associated with the topical application of prostaglandin analogs.

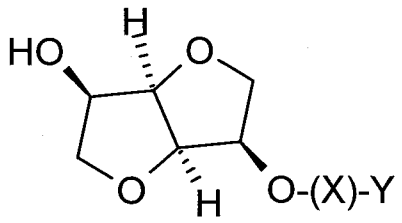
Accordingly, these combinations are useful as therapeutic agents for treating

glaucoma and ocular hypertension by lowering intraocular pressure.

Therefore, the present invention provides effective ophthalmic compositions for treating and/or preventing glaucoma and ocular hypertension having reduced side effects and, thereby, enhanced patient compliance.

The present invention relates to compositions comprising

(i) a nitric oxide releasing isomannide derivative of the following formula (I) or a stereoisomer thereof:



(I)

X is -CO- or -COO-;

Y is

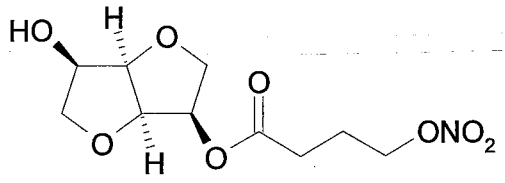
- straight or branched C_1-C_{10} alkyl chain, substituted with one or two $-ONO_2$; or
- C_1-C_6 alkylenoxy- C_1-C_5 alkyl wherein the alkyl group is substituted by one or two $-ONO_2$ groups.

(ii) a prostaglandin $F_{2\alpha}$ analog selected from the group consisting of latanoprost, bimatoprost, travoprost, tafluprost or unoprostone isopropyl, preferably the prostaglandin $F_{2\alpha}$ analog is travoprost or bimatoprost.

A preferred embodiment of the invention provides compositions comprising:

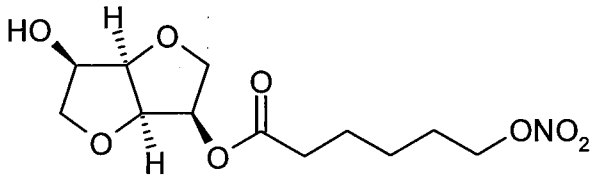
(i) a nitric oxide releasing isomannide derivative of formula (I) that is selected from the group:

- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 4-(nitrooxy) butanoate (Compound (1))



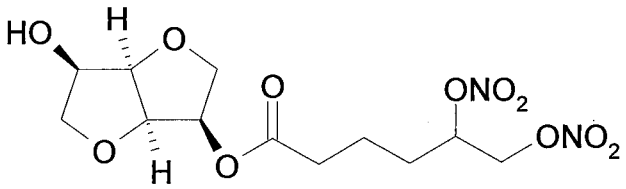
(1)

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



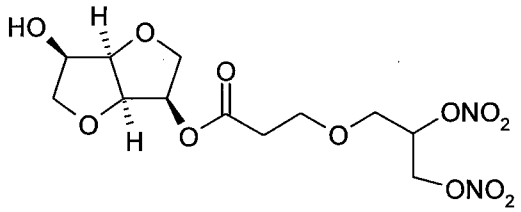
(2)

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



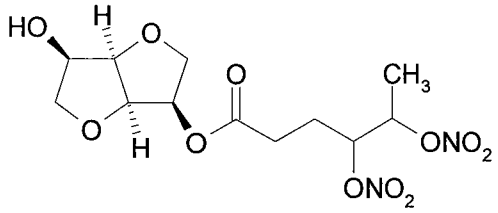
(3)

- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 3-(2,3-bis(nitrooxy)propoxy)propanoate (Compound (4))



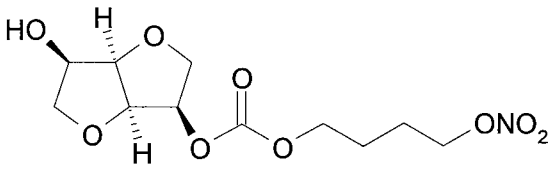
(4)

- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 4,5-bis (nitrooxy)hexanoate (Compound (5))



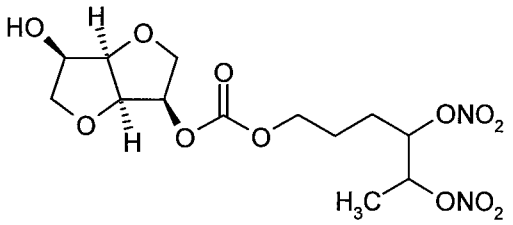
(5)

- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 4-(nitrooxy) butyl carbonate (Compound (6))



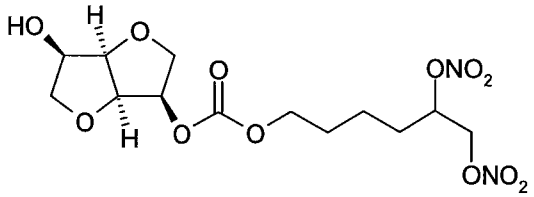
(6)

- 4,5-bis(nitrooxy)hexyl (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl carbonate (Compound (7))



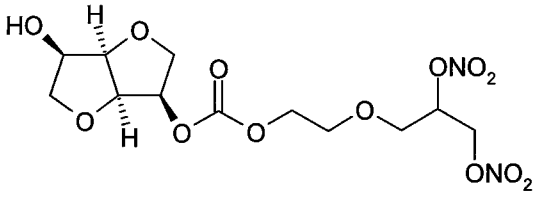
(7)

- 5,6-bis(nitrooxy)hexyl (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b] furan-3-yl carbonate (Compound (8))



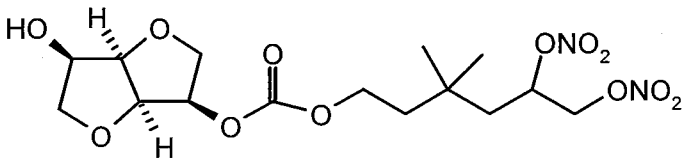
(8)

- 2-(2,3-bis(nitrooxy)propoxy)ethyl(3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl carbonate (Compound (9))



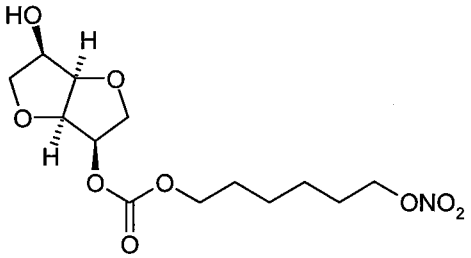
(9)

- 3,3-dimethyl-5,6-bis(nitrooxy)hexyl (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl carbonate (Compound (10))



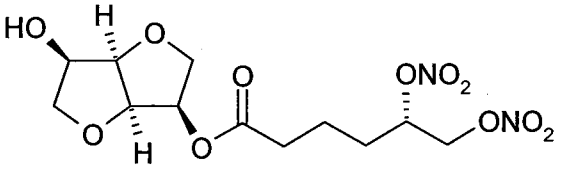
(10)

- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 6-(nitrooxy) hexyl carbonate (Compound (11))



(11)

- (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Compound (12))



(12)

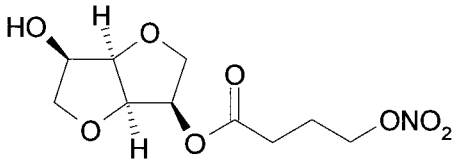
and stereoisomer thereof

(ii) a prostaglandin $F_{2\alpha}$ analog selected from the group consisting of: latanoprost, bimatoprost, travoprost, tafluprost and unoprostone isopropyl.

Another embodiment of the invention provides compositions comprising:

(i) a nitric oxide releasing isomannide derivative of formula (I) that is selected from the group:

- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 4-(nitrooxy) butanoate (Compound (1))



(1)

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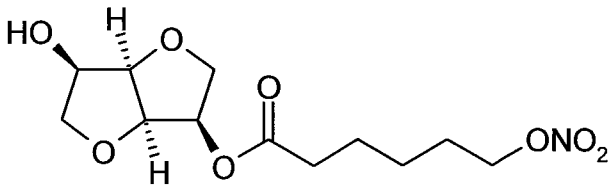

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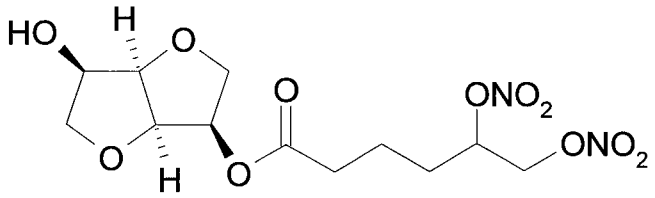
- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 5,6-bis (nitrooxy) hexanoate (Compound (3))



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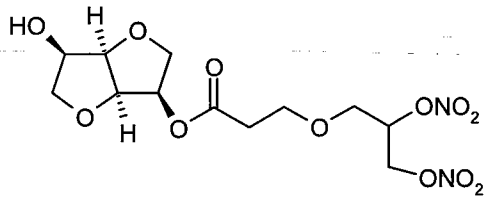
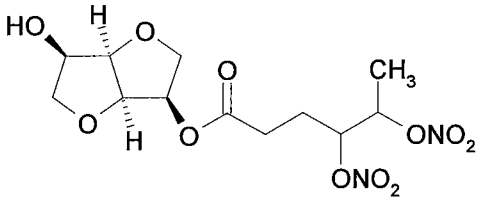


(4)

- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 4,5-bis (nitrooxy)hexanoate (Compound (5))



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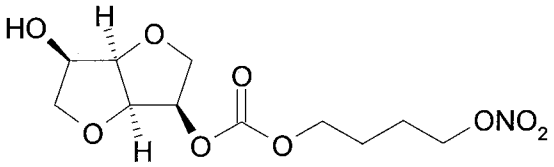
- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 4-(nitrooxy) butyl carbonate (Compound (6))



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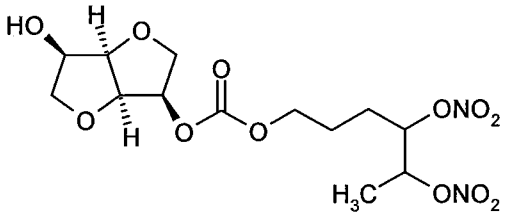

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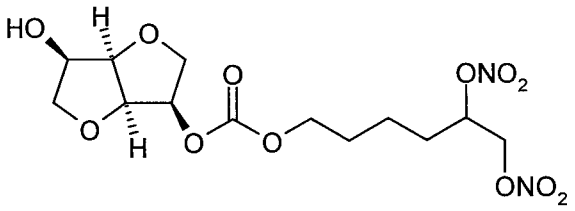

(8)

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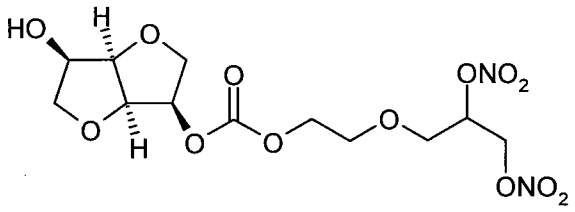
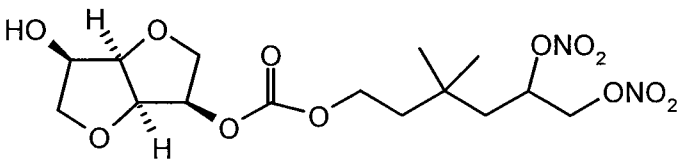


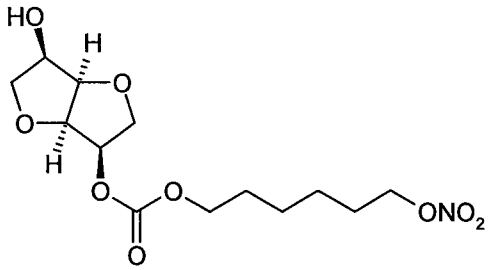
(9)

- 3,3-dimethyl-5,6-bis(nitrooxy)hexyl (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl carbonate (Compound (10))



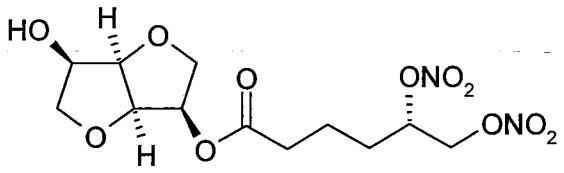
(10)

- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 6-(nitrooxy) hexyl carbonate (Compound (11))



(11)

- (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Compound (12))



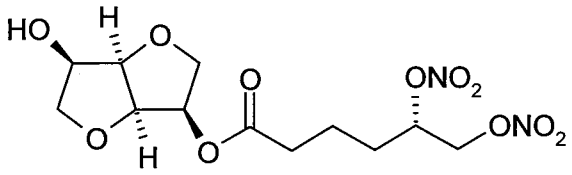
(12)

and stereoisomer thereof

(ii) a prostaglandin $F_{2\alpha}$ analog that is travoprost or bimatoprost.

Another embodiment of the invention provides compositions comprising:

(i) a nitric oxide releasing isomannide derivative of formula (I) that is - (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6- bis(nitrooxy)hexanoate (Compound (12))



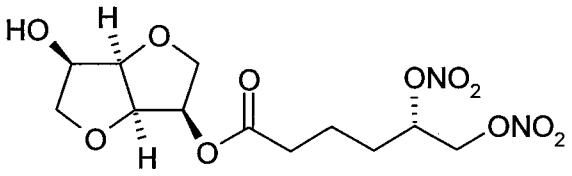
(12)

and

(ii) a prostaglandin $F_{2\alpha}$ analog that selected from the group consisting of latanoprost, bimatoprost, travoprost, tafluprost and unoprostone isopropyl.

Another embodiment of the invention provides compositions comprising:

(ii) a nitric oxide releasing isomannide derivative of formula (I) that is - (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6- bis(nitrooxy)hexanoate (Compound (12))



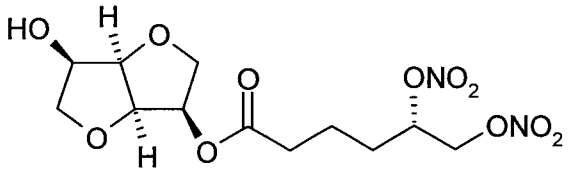
(12)

and

(ii) a prostaglandin $F_{2\alpha}$ analog that is travoprost.

Another embodiment of the invention provides compositions comprising:

(i) a nitric oxide releasing isomannide derivative of formula (I) that is - (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6- bis(nitrooxy)hexanoate (Compound (12))



(12)

and

(ii) a prostaglandin $F_{2\alpha}$ analog selected that is bimatoprost.

The weight ratio of the nitric oxide releasing isomannide derivative of formula (I) to the prostaglandin $F_{2\alpha}$ analog is generally 1:1 to 10000:1 and preferably is 5:1 to 1000:1.

The present invention also provides compositions comprising a nitric oxide releasing isomannide derivative of formula (I) and a prostaglandin $F_{2\alpha}$ analog as above defined, for the treatment of glaucoma, ocular hypertension and for reducing intraocular pressure associated with ocular diseases.

Another embodiment of the present invention provides ophthalmic pharmaceutical formulation comprising at least a nitric oxide releasing isomannide derivative of formula (I) as defined above, a prostaglandin $F_{2\alpha}$ analog and at least an ophthalmic excipient.

The ophthalmic excipients may include for example, buffers, tonicity agents, chelating agents, viscosity enhancers, solubilizing agents, surfactants, antioxidants, preservatives or ophthalmic vehicles.

The ophthalmic pharmaceutical formulation of the present invention can be in the form of solutions, suspensions, emulsions, dispersions, topical eye drops, or gel tears.

In general, ophthalmic pharmaceutical formulation of the present invention will include the compounds of formula (I) in an amount between about 0.001 and about 10% percent by weight (w/v %) and the prostaglandin $F_{2\alpha}$ analog in an amount between about 0.0001 and about 0.2 w/v %.

It is preferred to use nitric oxide releasing isomannide derivatives of formula (I) in an amount between about 0.005 and about 2.0 w/v %, and it is especially preferred to use an amount between about 0.01 and about 0.5 w/v %. It is preferred to use the prostaglandin $F_{2\alpha}$ analog in an amount between about 0.0001 and about 0.1 w/v %, depending on the potency of the prostaglandin.

A combination of a nitric oxide releasing isomannide derivative of formula (I) and a prostaglandin $F_{2\alpha}$ analog according to the present invention may be prepared in one dosage form comprising effective amounts of the respective compounds at a suitable mixing ratio or as a kit used by administering each preparation comprising an effective amount of each compound simultaneously or separately at an interval.

The nitric oxide releasing isomannide derivatives of formula (I) are described in EP 2 238 143B; this patent discloses structures, preparations and physical properties of these compounds.

The prostaglandin $F_{2\alpha}$ analogs used in the compositions of the invention have been known as agents for treatment of glaucoma and they are:

latanoprost is 5-heptenoic acid, 7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl]-, 1-methylethyl ester, (5*Z*)-;

bimatoprost is 5-heptenamide, 7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*S*)-3-hydroxy-5-phenyl-1-penten-1-yl]cyclopentyl]-*N*-ethyl-, (5*Z*)-;

travoprost is 5-heptenoic acid, 7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*R*)-3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-buten-1-yl]cyclopentyl]-, 1-methylethyl ester, (5*Z*)-;

tafluprost is 5-heptenoic acid, 7-[(1*R*,2*R*,3*R*,5*S*)-2-[(1*E*)-3,3-difluoro-4-

phenoxy-1-buten-1-yl]-3,5-dihydroxycyclopentyl]-, 1-methylethyl ester, (5*Z*)-;

unoprostone isopropyl is 5-heptenoic acid, 7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]-, 1-methylethyl ester, (5Z)-.

Latanoprost, bimatoprost, travoprost, tafluprost or unoprostone isopropyl are commercially available.

EXAMPLES

Example 1

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

The Intraocular pressure (IOP) lowering activity of the combination of compound (12) (0.1%) and travoprost (0.004%) was assessed in ocular normotensive rabbits.

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

IOP was measured using a pneumatonometer 30 CLASSIC™ before topical application (basal) and at different time points (30, 60, 120, 180, 240 and 300 min) thereafter. Travoprost (0.004%) or vehicle (5% cremophor-EL; 0.3% DMSO; 0.2 mg/ml BAC in PBS pH 6.0) were topically administered 5 minutes prior to compound (12) (0.1%) or vehicle (same as above) as eye drops into the conjunctiva pocket. Eyes were randomly assigned to different treatment groups. One drop of 0.4% oxybuprocaine hydrochloride (Novesine, Sandoz) was instilled in each eye immediately before each set of ocular pressure measurements.

Results are reported in the table in which the ocular hypotensive activity of the combination, of compound (12) and of travoprost are expressed as IOP change (at 30, 60, 120 and 300 minutes following topical administration) versus vehicle and versus IOP at basal (mean ± standard error).

The combination of compound (12) (0.1%) and travoprost (0.004%) results in increased IOP lowering activity compared to either compound (12) (0.1%) or

travoprost (0.004%) given alone. Moreover, the effects of the combination last significantly longer than either compound (12) (0.1%) alone or travoprost (0.004%) alone.

The above mentioned results revealed that an enhanced intraocular pressure lowering effect and improvement of the duration of intraocular pressure lowering action could be obtained by using a nitric oxide releasing isomannide derivative of formula (I) and a prostaglandin $F_{2\alpha}$ analog in combination. The intraocular pressure lowering effect is greater than simple additivity, especially at the longer durations.

Table 1: Intraocular pressure (IOP) lowering activity in ocular normotensive NZW rabbits

	IOP change (mmHg)				
	30 minutes	60 minutes	120 minutes	180 minutes	300 minutes
Compound (12)	-1.4±0.6	-2.1±0.4	-0.3± 0.3	0.1±0.5	1.1±0.8
Travoprost	-1.6±1.6	-0.9 ± 1.0	-1.1±1.2	-0.8±0.4	-0.6±0.1
Compound (12) + travoprost	-3.9±0.8	-2.6±0.9	-3.2±0.6	-3.4±0.5	-2.6±0.7

Example 2

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

The Intraocular pressure (IOP) lowering activity of the combination of compound (12) (0.3%) and travoprost (0.004%) was assessed in ocular hypertensive rabbits.

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

NZW rabbits were injected with 0.1 ml of hypertonic saline (5%) into the vitreous humor of both eyes. IOP was measured using a Tono-Pen AVIA Vet® at different time points (30, 60, 120 and 240 min) following hypertonic saline injection as well as before topical drug application (basal).

Travoprost (0.004%) or vehicle (5% cremophor-EL; 0.3% DMSO; 0.2 mg/ml BAC in PBS pH 6.0) were topically administered 15 min before hypertonic saline injection.

Compound (12) (0.3%) or vehicle (5% cremophor-EL; 0.3% DMSO; 0.2 mg/ml BAC in PBS pH 6.0) were topically administered immediately after hypertonic saline injection. Eyes were randomly assigned to different treatment groups.

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 effects (at 30, 60, 120 and 300 minutes following topical administration) of travoprost, compound (12) and the combination of compound (12) and travoprost are reported in table 2.

The results reported in table 2 are expressed as IOP change (at 30, 60, 120 and 300 minutes following topical administration) versus vehicle and versus IOP at basal (mean ± standard error).

The results show that the combination of compound (12) and travoprost has an increased IOP lowering activity compared to either compound (12) or travoprost given alone and that the combination of compound (12) and travoprost induces an enhanced and sustained intraocular pressure lowering effect at longer time points.

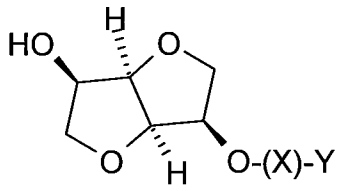
Table 2: Intraocular pressure (IOP) lowering activity in ocular hypertensive NZW rabbits

	IOP change (mmHg)			
	30 minutes	60 minutes	120 minutes	240 minutes
Travoprost	-2.4±0.5	-5.0±0.8	-5.1±0.7	-1.7±0.4
Compound (12)	-2.4±0.6	-7.7±0.5	-6.4±0.5	-1.8±0.6
Compound (12) + travoprost	-2.5±0.8	-9.6±1.0	-9.6±0.8	-3.2±0.7

CLAIMS

1. A composition comprising:

(i) a nitric oxide releasing isomannide derivative of the following formula (I) or a stereoisomer thereof:



(I)

X is -CO- or -COO-;

Y is

- straight or branched C_1-C_{10} alkyl chain, substituted with one or two -ONO_2; or
- C_1-C_6 alkylenoxy- C_1-C_5 alkyl wherein the alkyl group is substituted by one or two -ONO_2 groups.

(ii) a prostaglandin F2α analog selected from the group consisting of latanoprost, bimatoprost, travoprost, tafluprost or unoprostone isopropyl.

2. A composition according to claim 1 wherein the prostaglandin F2α analog is travoprost or bimatoprost.

3. A composition according to claims 1 or 2 wherein

(ii) the nitric oxide releasing isomannide derivative of formula (I) selected from the group:

- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 4-(nitrooxy) butanoate (Compound (1))
- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 6-(nitrooxy)hexanoate (Compound (2))
- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 5,6-bis

(nitrooxy) hexanoate (Compound (3))

- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 3-(2,3-bis(nitrooxy)propoxy)propanoate (Compound (4))
- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 4,5-bis (nitrooxy)hexanoate (Compound (5))
- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 4-(nitrooxy) butyl carbonate (Compound (6))
- 4,5-bis(nitrooxy)hexyl(3R,3aR,6R,6aR)-6-[3,2-b]furan-3-yl carbonate (Compound (7))
- 5,6-bis(nitrooxy)hexyl(3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b] furan-3-yl carbonate (Compound (8))
- 2-(2,3-bis(nitrooxy)propoxy)ethyl(3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl carbonate (Compound (9))
- 3,3-dimethyl-5,6-bis(nitrooxy)hexyl (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl carbonate (Compound (10))
- (3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl 6-(nitrooxy)hexyl carbonate (Compound (11))
- (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Compound (12))

and stereoisomer thereof.

4. A composition according to claim 1 wherein:

(i) the nitric oxide releasing isomannide derivative of formula (I) is - (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Compound (12)).

5. A composition according to claim 1 wherein:

(ii) the nitric oxide releasing isomannide derivative of formula (I) is - (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Compound (12))

(iii) the prostaglandin F2α analog is travoprost.

6. A composition according to claim 1 wherein:

(i) the nitric oxide releasing isomannide derivative of formula (I) is - (S)-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl) 5,6-bis(nitrooxy)hexanoate (Compound (12))

(ii) the prostaglandin F2α analog selected is bimatoprost.

7. The compositions according to any of claim 1 to 6 wherein the weight ratio of the nitric oxide releasing isomannide derivative of formula (I) to the prostaglandin F2α analog is 1:1 to 10000:1.

8. The compositions according to claim 7 wherein the weight ratio of the nitric oxide releasing isomannide derivative of formula (I) to the prostaglandin F2α analog is 5:1 to 1000:1.

9. The compositions according to any of claim 1 to 8 for use as medicament.

10. The compositions according to any of claim 1 to 8 for use in the treatment of glaucoma and ocular hypertension.

11. The compositions according to any of claim 1 to 8 for use in the reduction of intraocular pressure associated with ocular diseases.

12. Ophthalmic pharmaceutical formulations comprising a composition according to any of claims 1 to 8 and at least one ophthalmic excipient.

13. A kit comprising: a nitric oxide releasing isomannide derivative of formula (I) according to claim 1 and a prostaglandin F2α analog according to claim 1 for administering the compounds simultaneously or separately at an interval.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/076865

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/164 A61K31/191 A61K31/343 A61P27/02 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)
A61K

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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 386 611 A1 (TEIKA PHARMACEUTICAL CO LTD [JP]; KOWA CO [JP]) 4 February 2004 (2004-02-04) claims 1-3, 5, 6, 9, 10 -----	1-13
Y	WO 2014/063923 A1 (NICOX SA [FR]) 1 May 2014 (2014-05-01) cited in the application page 1, lines 1-3 page 17, lines 14-18 page 18, lines 3-4 ----- -/--	1-13

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 2016	04/02/2016

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1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	EP 2 238 143 B1 (NICOX SA [FR]) 15 August 2012 (2012-08-15) cited in the application compounds 1-25 paragraphs [0036], [0089] claims 9-11, 13, 14 -----	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/076865

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