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(54) Title: QUINONE BASED NITRIC OXIDE DONATING COMPOUNDS

(57) Abstract: The present invention relates to nitric oxide donor compounds having a quinone based structure, to processes for their preparation and to their use in the treatment and/or prophylaxis of glaucoma and ocular hypertension.

QUINONE BASED NITRIC OXIDE DONATING COMPOUNDS

The present invention relates to nitric oxide donor compounds of formula (I) for the use in the treatment and/or prophylaxis of glaucoma and ocular hypertension.

The present invention also relates to combinations comprising nitric oxide donor compounds of formula (I) and one or more further active ingredients for the use in the treatment and/or prophylaxis of glaucoma and ocular hypertension.

Glaucoma, including normotensive and hypertensive 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 untreated, may result in total blindness. Hypertensive glaucoma occurs when an imbalance in production and drainage of fluid in the eye (aqueous humor) increases eye pressure to unhealthy levels.

Conversely, normotensive glaucoma occurs despite the intraocular pressure is kept to reasonably low levels.

The loss of visual field, in one form of primary open angle glaucoma (POAG), is associated with a sustained increase in the intraocular pressure of the diseased eye. Moreover, elevated intraocular pressure without visual field loss is thought to be indicative of the early stages of this form of POAG.

Normotensive glaucoma is a chronic progressive optic neuropathy resulting in typical optic nerve head changes, retinal nerve fiber layer defects, and characteristic visual field defects. In addition, the chamber angle is open and IOP values within statistical normal limits (lower than 22 mmHg) (Lee et al. 1998; for review, see Hoyng and Kitazawa 2002). There is evidence that treatment of normotensive glaucoma by lowering IOP can slow the glaucomatous process. A reduction of at least 30% in IOP is needed to induce a favorable alteration in this disease.

Apart from both these main kinds of glaucoma other pathologies can lead to an elevation of IOP, namely secondary glaucoma including post-uveitic glaucoma and steroid-induced glaucoma. 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-blockers, α-agonists, cholinergic agents, carbonic anhydrase inhibitors, or prostaglandin analogs.

Several side effects are associated with the drugs conventionally used to treat glaucoma.

Topical beta-blockers show serious pulmonary side effects, depression, fatigue, confusion, impotence, hair loss, heart failure and bradycardia.

Topical α-agonists have a fairly high incidence of allergic or toxic reactions; topical cholinergic agents (miotics) can cause visual side effects.

The side effects associated with oral carbonic anhydrase inhibitors include fatigue, anorexia, depression, paresthesias and serum electrolyte abnormalities (The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, M. H. Beers and R. Berkow Editors, Sec. 8, Ch. 100).

Finally, the topical prostaglandin analogs (bimatoprost, latanoprost, travoprost, tafluprost and unoprostone) used in the treatment of glaucoma can produce ocular side effects, such as increased pigmentation of the iris, ocular irritation, conjunctival hyperaemia, iritis, uveitis and macular oedema (Martindale, Thirty-third edition, p. 1445).

Diseases of the macula, such as age-related macular degeneration and diabetic macular edema, account for major causes of blindness. The drugs currently used for treating diseases of the macula are steroidal anti-inflammatory drugs such as triamcinolone acetonide or fluocinolone. However intravitreal triamcinolone injections are associated with many ocular complications including elevation of intraocular pressure.

Elevated intraocular pressure is a common post-surgical complications following ocular surgery such as pars plana vitrectomy, vitreoretinal surgery, retinal detachment surgery, panretinal photocoagulation.

It is known that in the eye nitric oxide (NO) has an important role in certain physiological processes, e.g. regulation of aqueous humor dynamics, vascular tone, retinal 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.

US patent 4,590,207 discloses ophthalmic solution containing isosorbide mononitrate as an active ingredient for treating and/or preventing intraocular hypertension and glaucoma. US patent application 2002/0168424 discloses the use of a mixture of a nitric oxide (NO) donor such as nitrovasodilators like minoxidil, nitroglycerin, L-arginine, isosorbide dinitrate, or nitroprusside, and a cyclic guanosine 3',5'-monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5) inhibitor such as sildenafil citrate for treating glaucoma or ocular hypertension. The disclosed combinations promotes systemic vascular relaxation, enhanced blood flow to the optic nerve, dilation of the trabecular meshwork, the Schlemm's canal and uveoscleral outflow channel tissues, enhanced aqueous humor drainage and thus lowered intraocular pressure (IOP) in mammalian eye.

Organic nitrates have been used for over a century in the treatment of cardiac diseases however, it is known that the classical organic nitrates used in therapy, such as glycerol trinitrate, isosorbide dinitrate or isosorbide-5-mononitrate, undergo tolerance and lose their activity upon repeated administration. Nitrate tolerance develops despite an elevation in the drug plasma concentration reflecting a decrease in vascular sensitivity to previously therapeutic levels. This can be prevented or reduced by inclusion of a nitrate free period in the dosing schedule.

WO 2013/060673 discloses nitric oxide donor compounds having a quinone based structure and their use in the treatment of vascular diseases, in particular WO 2013/060673 discloses that these compounds have reduced tolerance and improve the muscle function of mdx mice which are genetically and biochemically homologous to human Duchenne Muscle Dystrophy.

Therefore, the technical problem underlying the present invention is to provide effective therapeutic agents for the use in the treatment and/or prophylaxis of hypertensive glaucoma, normotensive glaucoma secondary glaucoma and ocular

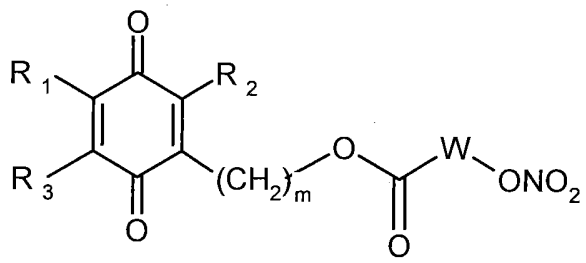
hypertension.

Surprisingly, it has now been found that the nitric oxide donors of the present invention lower intraocular pressure than that of nitric oxide donors described in the art.

It has also been surprisingly found that the nitric oxide donors of the present invention have additional beneficial anti-inflammatory and antioxidant properties that work synergistically with the delivery of nitric oxide to promote regulation of aqueous humor outflow through the trabecular meshwork, cells repairing and protection.

The present invention provides nitric oxide donors having a better pharmacological activity than that of nitric oxide donors described in the art.

The present invention relates to compounds of formula (I)



(I)

or stereoisomers thereof, wherein

R_1 is selected from H, methyl or methoxy,

R_3 is selected from H, methyl or methoxy,

or R_1 and R_3 together form –CH=CH-CH=CH-;

R_2 is H, methyl;

m is an integer from 1 to 10; preferably m is an integer from 3 to 10;

W is:

1) $-(Y)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

2) $-(Y)-(CH_2)_n-[X]-(CH_2)_{n1}-$

3) $-CH(NHR_5)-CH(R_4)-O(CO)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

wherein

Y is O or a covalent bond;

n is an integer from 1 to 10;

n1 is an integer from 1 to 10

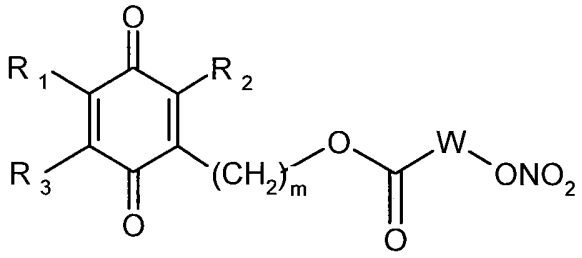
p is 0 or 1;

X is O, NH or S;

R_4 is H or methyl;

R_5 is H, $-C(O)CH_3$ or $-C(O)O-C(CH_3)_3$.

In another embodiment of the invention, there is provided a compound of formula (I) or stereoisomers thereof



(I)

or stereoisomers thereof, wherein

R_1 is methyl,

R_3 is methyl,

R_2 is methyl,

m is an integer from 1 to 10; preferably m is an integer from 3 to 10;

W is:

1) $-(Y)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

2) $-(Y)-(CH_2)_n-[X]-(CH_2)_{n1}-$

3) $-CH(NHR_5)-CH(R_4)-O(CO)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

wherein

Y is O or a covalent bond;

n is an integer from 1 to 10;

n1 is an integer from 1 to 10

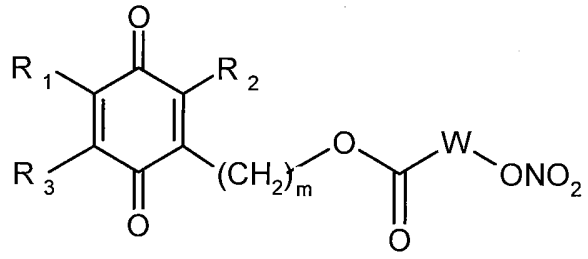
p is 0 or 1;

X is O, NH or S;

R_4 is H or methyl;

R_5 is H, $-C(O)CH_3$ or $-C(O)O-C(CH_3)_3$.

In another embodiment of the invention, there is provided a compound of formula (I) or stereoisomers thereof



(I)

or stereoisomers thereof, wherein

R_1 is methoxy,

R_3 is methoxy,

R_2 is methyl,

m is an integer from 1 to 10; preferably m is an integer from 3 to 10;

W is:

1) $-(Y)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

2) $-(Y)-(CH_2)_n-[X]-(CH_2)_{n1}-$

3) $-CH(NHR_5)-CH(R_4)-O(CO)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

wherein

Y is O or a covalent bond;

n is an integer from 1 to 10;

n1 is an integer from 1 to 10

p is 0 or 1;

X is O, NH or S;

R_4 is H or methyl;

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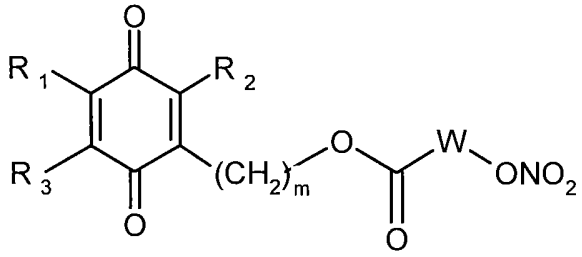
In another embodiment of the invention, there is provided a compound of formula (I) or stereoisomers thereof



(I)

or stereoisomers thereof, wherein

R_1 is methoxy,

R_3 is methoxy,

R_2 is methyl,

m is an integer from 1 to 10; preferably m is an integer from 3 to 10;

W is:

1) $-(Y)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

wherein

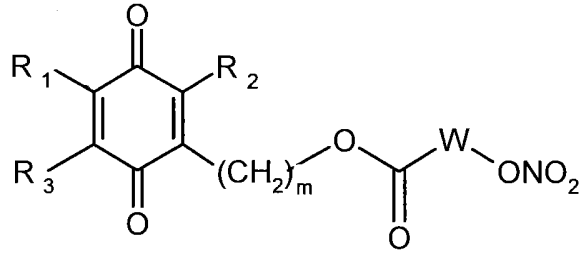
Y is O;

n is an integer from 1 to 10;

n1 is an integer from 1 to 10

p is 0 or 1.

In another embodiment of the invention, there is provided a compound of formula (I) or stereoisomers thereof



(I)

or stereoisomers thereof, wherein

R_1 is methoxy,

R_3 is methoxy,

R_2 is methyl,

m is an integer from 1 to 10; preferably m is an integer from 3 to 10;

W is:

1) $-(Y)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

wherein

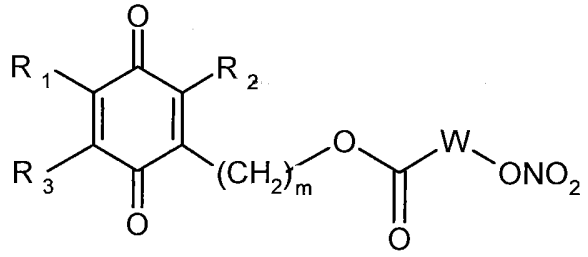
Y is a covalent bond;

n is an integer from 1 to 10;

n1 is an integer from 1 to 10

p is 0 or 1.

In another embodiment of the invention, there is provided a compound of formula (I) or stereoisomers thereof



(I)

or stereoisomers thereof, wherein

R_1 is methoxy,

R_3 is methoxy,

R_2 is methyl,

m is an integer from 1 to 10; preferably m is an integer from 3 to 10;

W is:

2) $-(Y)-(CH_2)_n-[X]-(CH_2)_{n1}-$

wherein

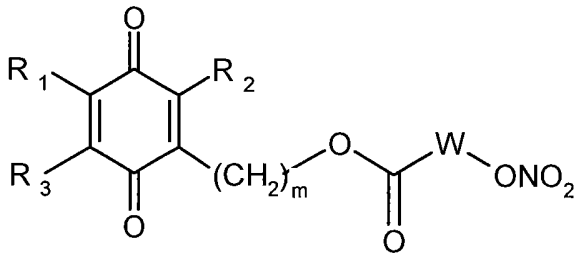
Y is covalent bond;

n is an integer from 1 to 10;

n1 is an integer from 1 to 10

X is O or NH.

In another embodiment of the invention, there is provided a compound of formula (I) or stereoisomers thereof



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or stereoisomers thereof, wherein

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R_2 is methyl,

m is an integer from 1 to 10; preferably m is an integer from 3 to 10;

W is:

2) $-(Y)-(CH_2)_n-[X]-(CH_2)_{n1}-$

wherein

Y is O;

n is an integer from 1 to 10;

n1 is an integer from 1 to 10

X is O or NH.

In another embodiment of the invention, there is provided a compound of formula (I) or stereoisomers thereof

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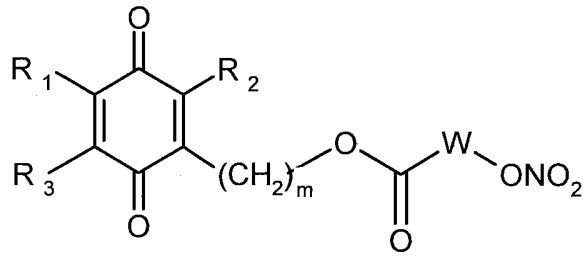


(I)

or stereoisomers thereof, wherein

R_1 is methoxy,

R_3 is methoxy,

R_2 is methyl,

m is an integer from 1 to 10; preferably m is an integer from 3 to 10;

W is:

3) $-CH(NHR_5)-CH(R_4)-O(CO)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

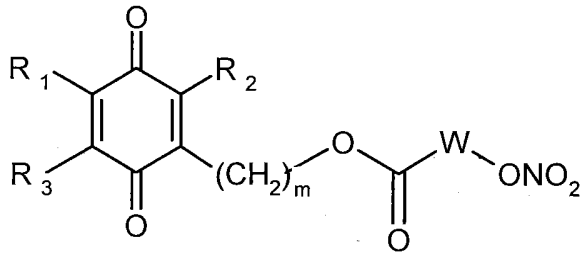
wherein

p is 0 or 1;

R_4 is H or methyl;

R_5 is H, $-C(O)CH_3$ or $-C(O)O-C(CH_3)_3$.

In another embodiment of the invention, there is provided a compound of formula (I) or stereoisomers thereof



(I)

or stereoisomers thereof, wherein

R_1 is methyl,

R_3 is methyl,

R_2 is methyl,

m is an integer from 1 to 10; preferably m is an integer from 3 to 10;

W is:

1) –(Y)-$(CH_2)_n$-[$CH(ONO_2)$]$_p$-CH_2-

wherein

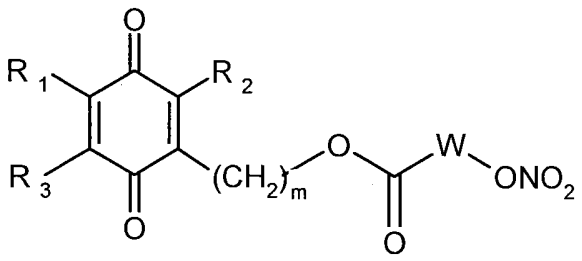
Y is O;

n is an integer from 1 to 10;

n1 is an integer from 1 to 10

p is 0 or 1.

In another embodiment of the invention, there is provided a compound of formula (I) or stereoisomers thereof



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or stereoisomers thereof, wherein

R_1 is methyl,

R_3 is methyl,

R_2 is methyl,

m is an integer from 1 to 10; preferably m is an integer from 3 to 10;

W is:

1) –(Y)-$(CH_2)_n$-[$CH(ONO_2)$]$_p$-CH_2-

wherein

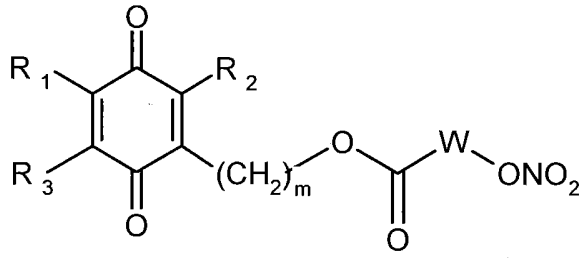
Y is a covalent bond;

n is an integer from 1 to 10;

n1 is an integer from 1 to 10

p is 0 or 1.

In another embodiment of the invention, there is provided a compound of formula (I) or stereoisomers thereof



(I)

or stereoisomers thereof, wherein

R_1 is methyl,

R_3 is methyl,

R_2 is methyl,

m is an integer from 1 to 10; preferably m is an integer from 3 to 10;

W is:

2) $-(Y)-(CH_2)_n-[X]-(CH_2)_{n1}-$

wherein

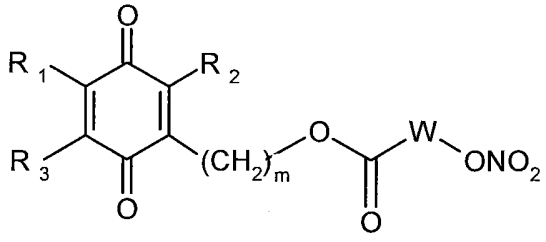
Y is covalent bond;

n is an integer from 1 to 10;

n1 is an integer from 1 to 10

X is O or NH.

In another embodiment of the invention, there is provided a compound of formula (I) or stereoisomers thereof



(I)

or stereoisomers thereof, wherein

R_1 is methyl,

R_3 is methyl,

R_2 is methyl,

m is an integer from 1 to 10; preferably m is an integer from 3 to 10;

W is:

2) $-(Y)-(CH_2)_n-[X]-(CH_2)_{n1}-$

wherein

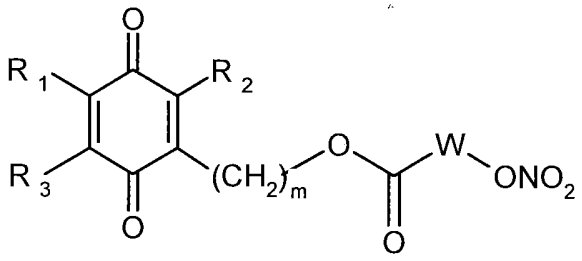
Y is O;

n is an integer from 1 to 10;

n1 is an integer from 1 to 10

X is O or NH.

In another embodiment of the invention, there is provided a compound of formula (I) or stereoisomers thereof



(I)

or stereoisomers thereof, wherein

R_1 is methyl,

R_3 is methyl,

R_2 is methyl,

m is an integer from 1 to 10; preferably m is an integer from 3 to 10;

W is:

3) $-CH(NHR_5)-CH(R_4)-O(CO)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

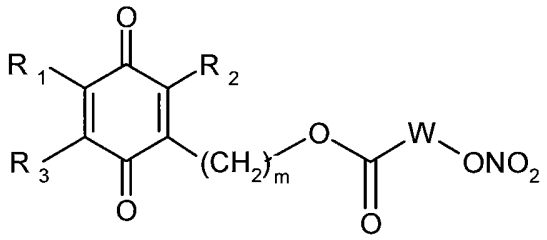
wherein

p is 0 or 1;

R_4 is H or methyl;

R_5 is H, -C(O)CH_3 or -C(O)O-C(CH_3)$_3$.

The present invention relates to compounds of formula (I)



(I)

or stereoisomers thereof, wherein

R_1 and R_3 together form –CH=CH-CH=CH-;

R_2 is methyl;

m is an integer from 1 to 10; preferably m is an integer from 3 to 10;

W is:

1) –(Y)-$(CH_2)_n$-[CH(ONO_2)]$_p$-CH_2-

2) –(Y)-$(CH_2)_n$-[X]-$(CH_2)_{n1}$-

3) –CH(NHR_5)-CH(R_4)-O(CO)-$(CH_2)_n$-[CH(ONO_2)]$_p$-CH_2-

wherein

Y is O or a covalent bond;

n is an integer from 1 to 10;

n1 is an integer from 1 to 10

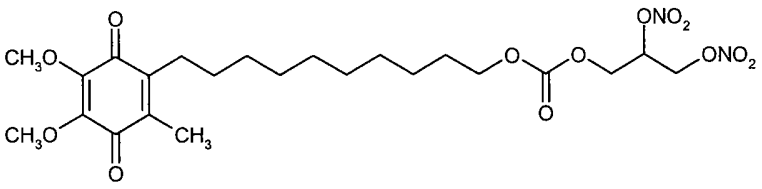
p is 0 or 1;

X is O, NH or S;

R_4 is H or methyl;

R_5 is H, -C(O)CH_3 or -C(O)O-C(CH_3)$_3$.

Another embodiment of the invention provides a compound of formula (I) selected from the group:



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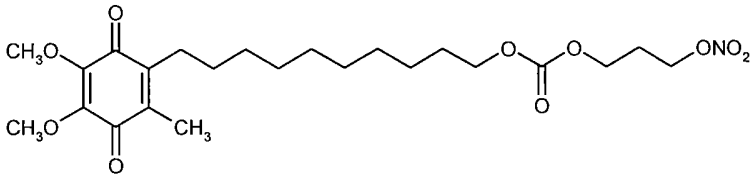

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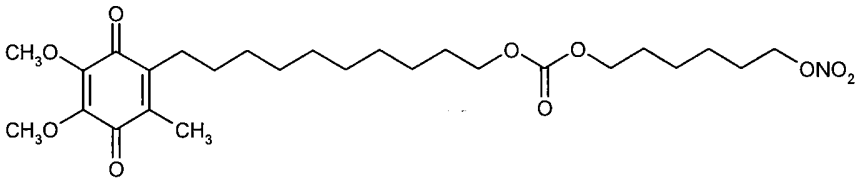

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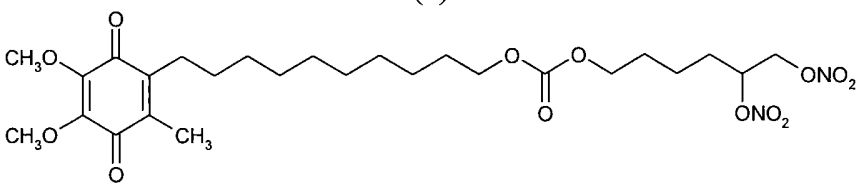

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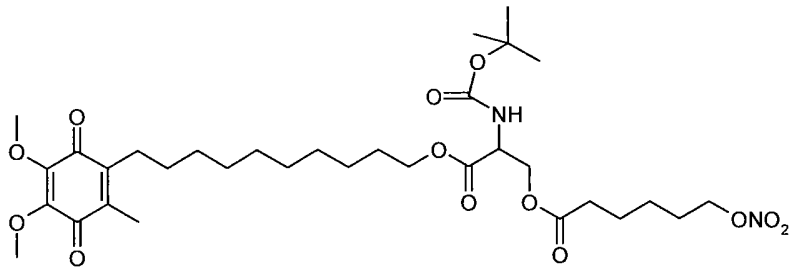

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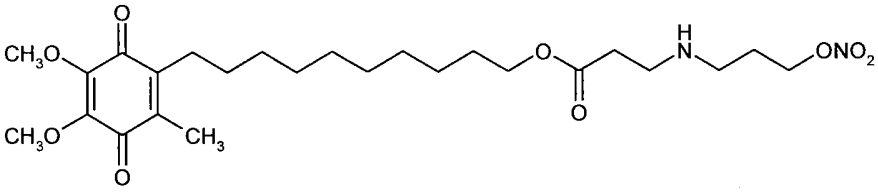

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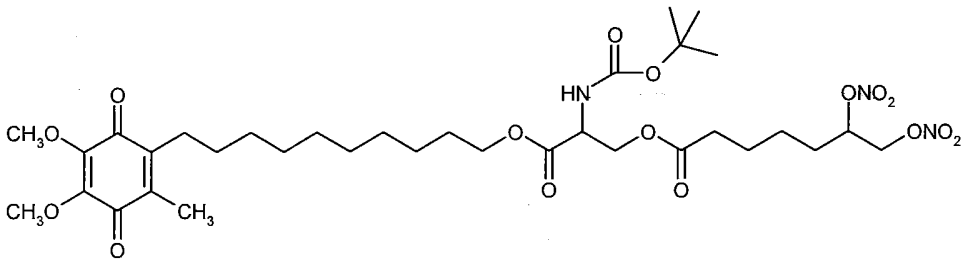

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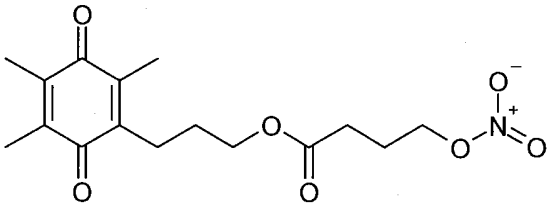

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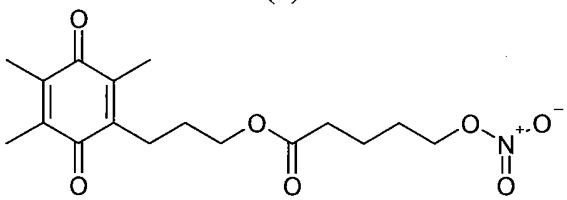

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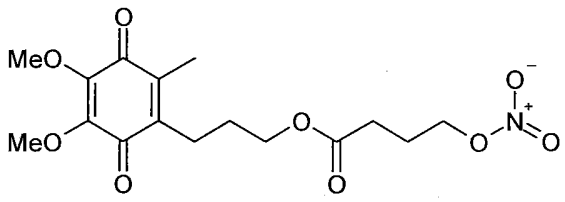

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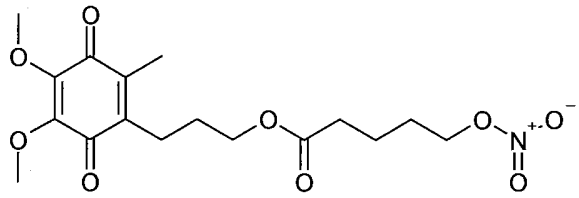

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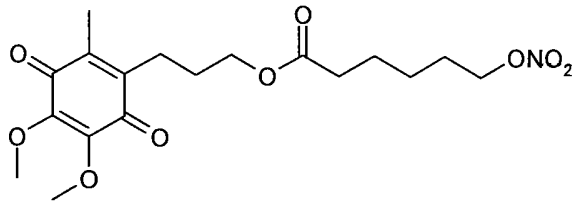

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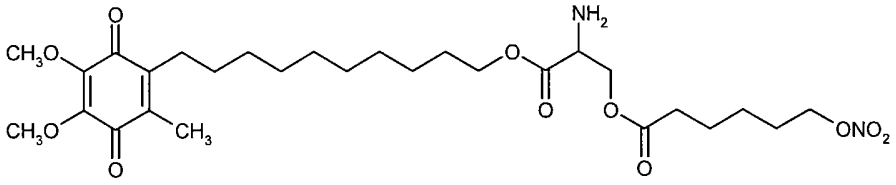

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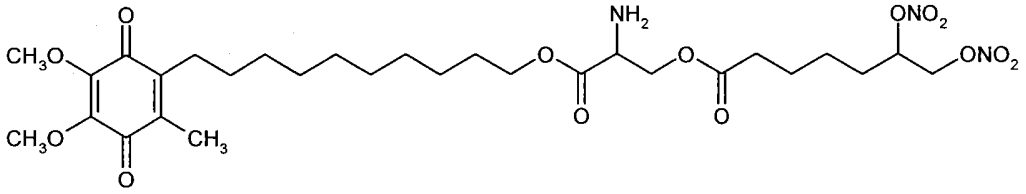


(14)

The present invention also relates to compounds of formula (I) or stereoisomers thereof for use in treating hypertensive glaucoma, normotensive glaucoma, secondary glaucoma and ocular hypertension.

Furthermore the present invention relates to compounds of formula (I) for the use in the treatment and/ or prophylaxis of age related macular degeneration, diabetic retinopathy, retinal vein occlusion, macular degeneration, inflammatory retinal disease, uveitis.

Another embodiment of the present invention to compounds of formula (I) for the treatment of high intraocular pressure resulting from orbital edema, post-surgical complications, intraocular inflammation and pupillary block or idiopathic causes.

The present inventions also relates to compositions comprising a nitric oxide donor of formula (I) in combination with one or more further active ingredients selected from the group consisting of alpha adrenergic agonist, beta blocker, carbonic anhydrase inhibitor, prostaglandin analogs, non-steroidal anti-inflammatory drugs, steroidal anti-

inflammatory drugs.

Examples of suitable alpha adrenergic agonist are brimonidine, apraclonidine, clonidine.

Examples of suitable beta blocker are timolol, carteolol, betaxolol, levobunolol.

Examples of suitable carbonic anhydrase inhibitor are dorzolamide, acetazolamide, brinzolamide, dorzolamide, dichlorphenamide, methazolamide.

Examples of suitable prostaglandin analogs are bimatoprost, latanoprost, travoprost, unoprostone and tafluprost.

Examples of non-steroidal anti-inflammatory drugs are bromfenac, flurbiprofen, naproxen, ketoprofen.

Examples of steroidal anti-inflammatory drugs are dexamethasone, fluocinolone acetonide, triamcinolone acetonide, budesonide, prednisolone.

Another embodiment of the present invention is a composition above reported for use in the treatment and/or prophylaxis of hypertensive glaucoma, normotensive glaucoma, secondary glaucoma and ocular hypertension.

Another embodiment of the present invention is a composition above reported for use in the treatment and/ or prophylaxis of secondary glaucomas, age related macular degeneration, diabetic retinopathy, macular degeneration, inflammatory retinal disease, uveitis.

Another embodiment of the present invention is a composition above reported for use in the treatment of high intraocular pressure resulting from orbital edema, post-surgical complications, intraocular inflammation, pupillary block, or idiopathic causes.

Another embodiment of the present invention provides pharmaceutical formulation for topical, periocular or intraocular administration comprising at least a nitric oxide donor of formula (I) and at least an ophthalmically acceptable component and/or ophthalmically acceptable vehicle.

Another embodiment of the present invention provides pharmaceutical formulation for topical, periocular or intraocular administration comprising at least a

nitric oxide donor of formula (I) one or more further active ingredients selected from the group consisting of alpha adrenergic agonist, beta blocker, carbonic anhydrase inhibitor, prostaglandin analogs, non-steroidal anti-inflammatory drugs, steroidal anti-inflammatory drugs and at least an ophthalmically acceptable component and/or ophthalmically acceptable vehicle.

The preferred route of administration of the compounds and compositions of the present invention is topical or intravitreal. The compounds and compositions of the present invention can be administered as solutions, suspensions, or emulsions (dispersions) for topical use.

The compounds for use in the current invention can also be administered via periocular administration, and may be formulated in solutions or suspensions for periocular administration. Formulations useful for periocular administration will generally be periocular injection formulations or surgical irrigating solutions. Periocular administration refers to administration to tissues near the eye, such as administration to the tissues or spaces surrounding the eyeball and within the orbit. Periocular administration can take place by injection, deposit, or any other mode of placement.

The compounds and the compositions of the present invention compositions may be formulated in solutions or suspensions for intraocular administration. Compositions useful for intraocular administration will generally be intraocular injection compositions or surgical irrigating solutions.

An "ophthalmically acceptable" component refers to a component which will not cause any significant ocular damage or ocular discomfort at the intended concentration and over the time of intended use. Solubilizers and stabilizers should be non-reactive. An "ophthalmically acceptable vehicle" refers to any substance or combination of substances which are non-reactive with the compounds and suitable for administration to a patient.

The nitric oxide donors of the present invention will generally be contained in the topical, periocular, or intraocular formulations contemplated herein in an amount of from about 0.001 to about 10.0% weight/volume. Preferred concentrations will range from

about 0.1 to about 5.0% w/v.

General synthesis

1. The compound of formula (I) wherein R_1 R_2 R_3 and m are as above defined, W is:

1) $-(Y)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

2) $-(Y)-(CH_2)_n-[X]-(CH_2)_{n1}-$

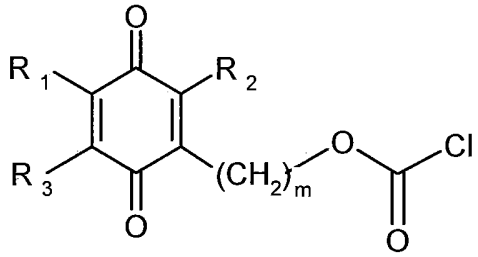
wherein

Y is O

n, n1, p are as above defined,

X is O, NH or S;

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



(II)

wherein R_1 R_2 R_3 and m are as above defined, with a compound of formula (III), (IV) or (IVa)

(III) $HO-(CH_2)_n-[CH(ONO_2)]_p-CH_2-ONO_2$

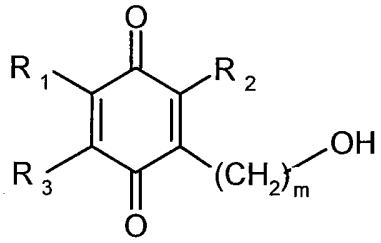
(IV) $HO-(CH_2)_n-[X]-(CH_2)_{n1}-ONO_2$

(IVa) $HO-(CH_2)_n-[N\text{-}Boc]-(CH_2)_{n1}-ONO_2$

wherein n, n1, p and X are as above defined and Boc is the t-butyl Carbamate group, in the presence of an organic or inorganic base as known for carbonate formation.

1.a Compounds of formula (III), (IV) and (IVa) are known in the literature or can be prepared by known methods (see for example Cena, C. et al, in *Bioorganic & Medicinal Chemistry* 2008, *16*, 5199–5206).

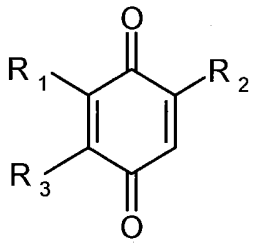
1.b Compounds of formula (II) can be prepared by reacting a compound of formula (V),



(V)

wherein R_1 R_2 R_3 and m are as above defined, with phosgene or triphosgene in the presence of an organic or inorganic base, in solvent such as CH_2Cl_2, chloroform, toluene, at temperature between -10 and 50°C as known in the literature for chlorocarbonate formation.

1.c Compounds (V) are known in the literature or can be prepared by the corresponding quinone, known in the literature, of formula (VI)



(VI)

Compounds (VI) wherein R_2 is H or methyl and R_1 and R_3 are methoxy or R_1 and R_3 taken together form –CH=CH-CH=CH- are commercially available. Compounds (VI) wherein R_1 and R_2 and R_3 are methyl are known in the literature and can be prepared from commercially available compounds (see for example Duveau D. Y. Bioor & Med Chemistry 2010, *18*, 6429–6441). Compounds (VI) wherein R_2 is methyl and R_1 and R_3 are different and are methyl or methoxy are known in the literature and can be prepared from commercially available compounds (see for example Duveau D. Y. Bioor & Med Chemistry 2010, *18*, 6429–6441).

2. The compound of formula (I) wherein R_1 R_2 R_3 and m are as above defined and W is:

1) $–(Y)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

2) –(Y)-$(CH_2)_n$-[X]-$(CH_2)_{n1}$-

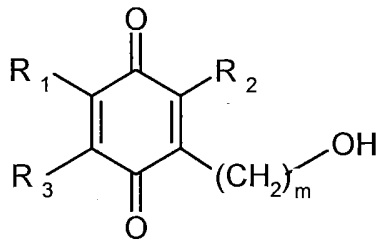
wherein

Y is a covalent bond;

n, n1, p are as above defined,

X is O, NH or S;

can be prepared by reacting compounds of formula (V),



(V)

above defined, with a compound of formula (VII), (VIII) or (VIIIa),

(VII) HOOC-$(CH_2)_n$-[$CH(ONO_2)$]$_p$-CH_2-ONO_2

(VIII) HOOC-$(CH_2)_n$-[X]-$(CH_2)_{n1}$-ONO_2

(VIIIa) HOOC-$(CH_2)_n$-[N-Boc]-$(CH_2)_{n1}$-ONO_2

in a aprotic polar/non polar solvent such as THF, DMF or CH_2Cl_2, in presence of DCC, EDAC, HBTU, HATU or other coupling reagents, in presence of catalytic amount of DMAP at temperature ranging from -0°C to 80°C. Eventually removing the Boc protecting group with acid treatment as known in the literature.

2.a Compound (V) can be prepared as reported above under paragraph 1.c).

2.b Compounds of formula (VII) and (VIII) and (VIIIa) are known in the literature or can be prepared from the corresponding alcohols of formulas (III) (IV) and (IVa) by oxidation with known agents such as TEMPO.

(III) HO-$(CH_2)_n$-[$CH(ONO_2)$]$_p$-CH_2-ONO_2

(IV) HO-$(CH_2)_n$-[X]-$(CH_2)_{n1}$-ONO_2

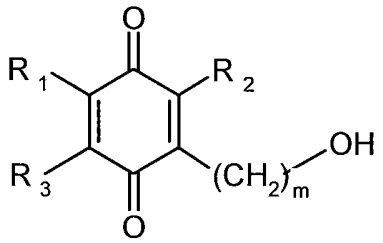
(IVa) HO-$(CH_2)_n$-[N-Boc]-$(CH_2)_{n1}$-ONO_2

3. The compounds of formula (I) wherein R_1 R_2 R_3 and m are as above defined

and W is:

3) $-CH(NHR_5)-CH(R_4)-O(CO)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

wherein n, p, R_4 are as above defined and R_5 is $-C(O)CH_3$ or $-C(O)O-C(CH_3)_3$ can be prepared by reacting a compound of formula (V) above defined



(V)

with a compound of formula (IX)

$HOOC-CH(NHR_5)-CH(R_4)-O(CO)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-ONO_2$

(IX)

wherein n, p, R_4 are as above defined and R_5 is $-C(O)CH_3$ or $-C(O)O-C(CH_3)_3$ in an aprotic polar/non polar solvent such as THF, DMF or CH_2Cl_2, in presence of DCC, EDAC, HBTU, HATU or other coupling reagents, in presence of catalytic amount of DMAP at temperature ranging from -0°C to 80°C.

3.a Compound (IX) can be prepared by reacting a compound of formula (VII), wherein n, and p are as above defined,

(VII) $HOOC-(CH_2)_n-[CH(ONO_2)]_p-CH_2-ONO_2$

with a compound of formula (X))

$HOOC-CH(NHR_5)-CH(R_4)-OH$

(X)

wherein R_4 and R_5 are as above defined, in an aprotic polar/non polar solvent such as THF, DMF or CH_2Cl_2, in presence of DCC, EDAC, HBTU, HATU or other coupling reagents, in presence of catalytic amount of DMAP at temperature ranging from -0°C to 80°C.

3.b Compound (X) are commercially available.

3.c Compound (V) can be prepared as reported above under paragraph 1.c.

4. The compounds of formula (I) wherein R_1 R_2 R_3 and m are as above defined and W is:

3) $-CH(NHR_5)-CH(R_4)-O(CO)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

wherein n, t, R_4 are as above defined and R_5 is –H

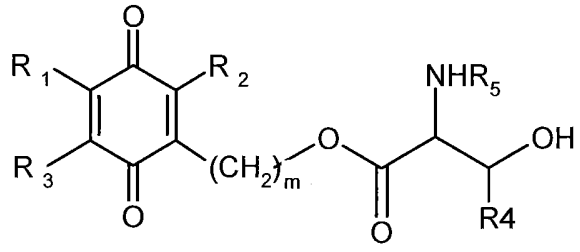
can be prepared by reacting the corresponding compounds of formula (I) prepared as described above under paragraph 3) with organic or inorganic acid to remove the Boc protecting group as known in the literature.

5. Alternatively the compounds of formula (I) wherein R_1 R_2 R_3 and m are as above defined and W is:

3) $-CH(NHR_5)-CH(R_4)-O(CO)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

wherein n, t, R_4 are as above defined and R_5 is $-C(O)CH_3$ or $-C(O)O-C(CH_3)_3$

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



(XI)

wherein R_1, R_2, R_3, R_4 m and R_5 are as above defined, with a compound of formula (X)

$HOOC-(CH_2)_n-[CH(ONO_2)]_p-CH_2-ONO_2$

(VII)

wherein n, p are as above defined, in an aprotic polar/non polar solvent such as THF, DMF or CH_2Cl_2, in presence of DCC, EDAC, HBTU, HATU or other coupling reagents, in presence of catalytic amount of DMAP at temperature ranging from -0°C to 80°C.

5.a Compound of formula (XI) can be prepared by reacting a compound of

formula (V) above defined with compounds of formula (XII)

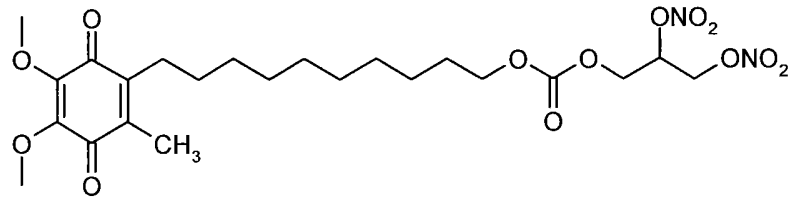
$$HOOC–CH(NHR_5)-CH(R_4)-OPG$$

(XII)

wherein R_4 and R_5 are as above defined and PG is an oxygen protective group such as the THP ether, in an aprotic polar/non polar solvent such as THF, DMF or CH_2Cl_2, in presence of DCC, EDAC, HBTU, HATU or other coupling reagents, in presence of catalytic amount of DMAP at temperature ranging from -0°C to 80°C, eventually removing the THP protective group with known methods.

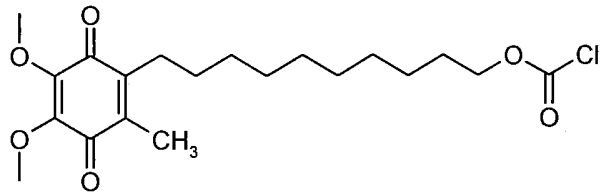
Example 1

Synthesis of 2,3-bis(nitrooxy)propyl 10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)decyl carbonate (Compound (1))



(1)

Step 1: Synthesis of 10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)decyl carbonochloridate



To a mixture of triphosgene (0.50 g; 1.7 mmol) and Na_2CO_3 (0.17 g; 1.6 mmol) in Toluene (10 ml) cooled at 0°C, a solution of 2-(10-hydroxydecyl)-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione (idebenone) (0.5 g; 1.5 mmol) was added dropwise. The mixture was stirred at 0°C for 8 hours, the precipitate was removed by filtration and the solution was used for the next step without any further purification.

Step 2: Synthesis of 2,3-bis(nitrooxy)propyl 10-(4,5-dimethoxy-2-methyl-3,6-

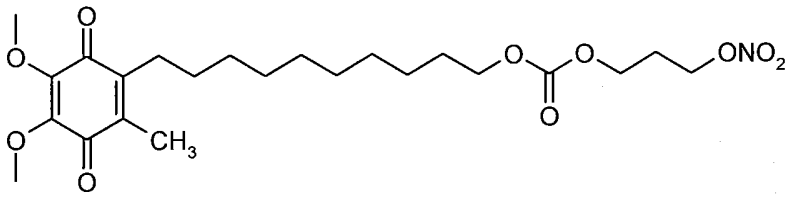
dioxocyclohexa-1,4-dien-1-yl)decyl carbonate

A solution of 10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)decyl carbonochloridate (obtained in Step 1) (1.5 mmol) was dropped into a solution of 3-hydroxypropane-1,2-diyl dinitrate (obtained as described by Dunstan, I et al. In *J. Chem. Soc.* 1965, 1319–1324)(2.1 mmol) and pyridine (0.17 ml, 2.1 mmol) in Toluene (10 ml) at room temperature. The mixture was stirred overnight at room temperature then was washed with a solution of citric acid at 10% (5 ml) and brine (5 ml), dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Eluent: petroleum ether/EtOAc 95/5) affording 150 mg (yield: 17%) of the title compound as an orange oil.

^{1}H-NMR ($CDCl_3$): δ, 5.54 – 5.48 (1H, m); 4.84 (1H, dd, J_1 = 3.6 Hz, J_2 = 6.3 Hz); 4.68 (1H, dd, J_1 = 6.3 Hz, J_2 = 6.6 Hz); 4.51 (1H, dd, J_1 = 3.9 Hz, J_2 = 8.4 Hz); 4.35 (1H, dd, J_1 = 5.4 Hz, J_2 = 6.9 Hz); 4.17 (2H, t, J = 6.6 Hz); 3.99 (6H, s); 2.47 – 2.42 (2H, m); 2.01 (3H, s); 1.73 – 1.63 (2H, m); 1.29 (14H, m).

Example 2

Synthesis of 10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)decyl 3-(nitrooxy)propyl carbonate (Compound (2))



(2)

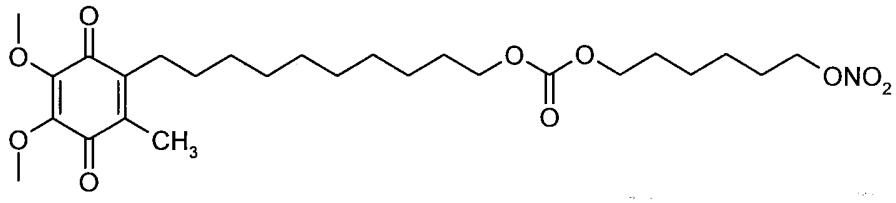
A solution of 10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)decyl carbonochloridate (obtained as described in Example 1, Step 1) (1.5 mmol) was added dropwise into a solution of 3-hydroxypropyl nitrate obtained as described by Cena, C. et al, in *Bioorganic & Medicinal Chemistry* 2008, *16*, 5199–5206) (2.1 mmol) and pyridine (0.17 ml, 2.1 mmol, in toluene (10 ml) at room temperature. The mixture was stirred overnight at room temperature then it was washed with a solution of citric acid at 10% (5

ml) and brine (5 ml), dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Eluent: petroleum ether/EtOAc 8/2) affording 206 mg (yield: 30%) of the title compound as an orange oil.

^{1}H-NMR ($CDCl_3$): δ, 4.58 (2H, t, J = 6.3 Hz); 4.25 (2H, t, J = 6.0 Hz); 4.14 (2H, t, J = 6.8 Hz); 3.99 (6H, s); 2.47 – 2.42 (2H, m); 2.16 – 2.10 (2H, m); 2.01 (3H, s); 1.72 – 1.62 (2H, m); 1.35 – 1.29 (14H, m).

Example 3

Synthesis of 10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)decyl 6-(nitrooxy)hexyl carbonate (Compound (3))



(3)

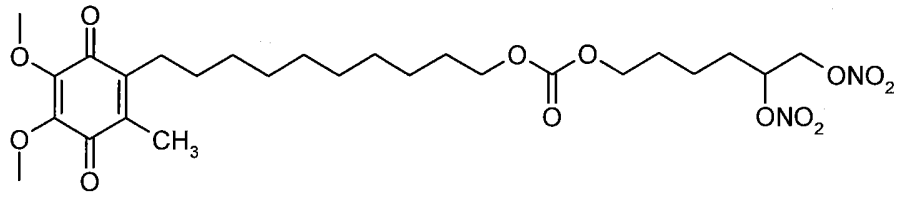
A solution of 10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)decyl carbonochloridate (obtained as described in Example 1, Step 1) (1.5 mmol) was added dropwise into a solution of 6-hydroxyhexyl nitrate obtained as described by Cena, C. et al, in *Bioorganic & Medicinal Chemistry* 2008, *16*, 5199–5206) (2.1 mmol) and pyridine (0.17 ml, 2.1 mmol) in Toluene (10 ml) at room temperature. The mixture was stirred overnight at room temperature then was washed with a solution of citric acid at 10% (5 ml) and brine (5 ml), dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Eluent: petroleum ether/EtOAc 9/1) affording 300 mg (yield: 38%) of the title compound as an orange oil.

^{1}H-NMR ($CDCl_3$): δ, 4.46 (2H, t, J = 6.4 Hz); 4.16 – 4.10 (4H, m); 3.99 (6H, s); 2.45 – 2.43 (2H, m); 2.01 (3H, s); 1.77 – 1.67 (4H, m); 1.45 – 1.44 (2H, m); 1.34 – 1.29 (14H, m).

Example 4

Synthesis of 5,6-bis(nitrooxy)hexyl 10-(4,5-dimethoxy-2-methyl-3,6-

dioxocyclohexa-1,4-dien-1-yl)decyl carbonate (Compound (4))



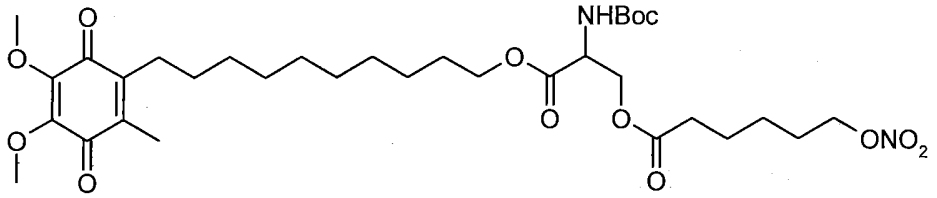
(4)

A solution of 10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)decyl carbonochloridate (obtained as described in Example 1, Step 1) (1.5 mmol) was added dropwise into a solution of 6-hydroxyhexane-1,2-diyl dinitrate (obtained as described by Cena, C. et al, in *Bioorganic & Medicinal Chemistry* **2008**, *16*, 5199–5206) (2.1 mmol) and pyridine (0.17 ml, 2.1 mmol) in toluene (10 ml) at room temperature. The mixture was stirred overnight at room temperature then was washed with a solution of citric acid at 10% (5 ml) and brine (5 ml), dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Eluent: petroleum ether/EtOAc 85/15) affording 318 mg (yield: 36%) of the title compound as an orange oil.

^{1}H-NMR ($CDCl_3$): δ, 5.39 – 5.32 (1H, m); 4.83 (1H, dd, J_1 = 6.0 Hz, J_2 = 9.9 Hz); 4.56 (1H, dd, J_1 = 6.6 Hz, J_2 = 6.3 Hz); 4.18 – 4.10 (4H, m); 3.99 (6H, s); 2.48 – 2.43 (2H, m); 2.01 (3H, s); 1.87 – 1.52 (8H, m); 1.36 – 1.30 (14H, m).

Example 5

Synthesis of [2-(tert-butoxycarbonylamino)-3-[10-(4,5-dimethoxy-2-methyl-3,6-dioxo-cyclohexa-1,4-dien-1-yl)decoxy]-3-oxo-propyl] heptanoate (Compound (5))



(5)

To a solution of 6-(nitrooxy)hexanoic acid (prepared as described by Ronsin, G. et

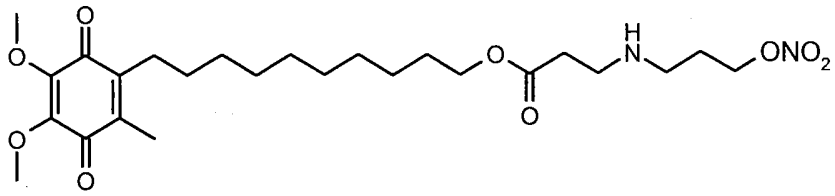
al. in WO2013/060673 A1, Example 2)(0.42 g, 2.2 mmol) in anhydrous CH_2Cl_2 (15 ml) cooled at 0°C, EDC·HCl (0.42 g, 2.2 mmol) and DMAP (catalytic amount) were added. The solution was stirred for 1 hour at room temperature. Then *N*-(*tert*-butoxycarbonyl)serine (0.45 g, 2.2 mmol) was added and the solution was stirred at r.t. for further 3 hours. The mixture was washed with water (2 x 10 ml), brine (1 x 10 ml), dried over Na_2SO_4 and evaporated under reduced pressure.

The residue was re-dissolved in anhydrous CH_2Cl_2 (15 ml), cooled at 0°C then EDC·HCl (0.46 mg, 2.4 mmol), DMAP (catalytic amount) and Idebenone (0.74 g, 2.2 mmol) were added. The mixture was stirred 4 hours at room temperature then was washed with water (2 x 10 ml), brine (1 x 10 ml), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent petroleum ether/EtOAc 10% to 20%), to afford the title compound as an orange oil (0.16 g, yield: 10%).

^{1}H-NMR ($CDCl_3$): δ, 5.30 – 5.28 (1H, m); 4.56 – 4.54 (1H, m); 4.44 (2H, t, J = 3.3 Hz); 4.36 – 4.31 (1H, m); 4.15 (2H, t, J = 6.8 Hz); 3.99 (6H, s); 2.47 – 2.42 (2H, m); 2.32 (2H, t, J = 7.5 Hz); 2.01 (3H, s); 2.18 – 1.57 (5H, m); 1.46 (9H, s); 1.40 – 1.16 (19H, m).

Example 6

Synthesis of 10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)decyl 3-(3-(nitrooxy)propylamino)propanoate (Compound (6)).



(6)

Step 1: Synthesis of N-[3-(nitrooxy)propyl]-ß-alanine nitric acid salt 0.4 g (2.7 mmol) of N-(3-hydroxypropyl)- ß -alanine (obtained as described by Pratt and co. in *J. Chem. Soc. Perk. Trans 1*, **1988**, 13) were added to 10 ml of fuming nitric acid cooled at -

15°C. The solution was allowed to reach r.t. and was kept under stirring for 18 hours. After that period the solvent was distilled under reduced pressure and the residue was dropped into 100 ml of diethyl ether at –15°C and triturated to obtain a white solid (0.45 g, 65%).

^{1}H-NMR (d_6-DMSO): δ, 8.51 (2H, s br); 4.60 (2H, s); 3.16 (2H, s); 3.06 (2H, s); 2.67 – 2.64 (2H,m); 2.04 (2H).

^{13}C-NMR (d6-DMSO): δ, 172.2; 71.2; 44.3; 43.1; 30.82; 23.5.

Step 2: Synthesis of 10-(4,5-dimethoxy-2-methyl-3,6-dioxo cyclohexa-1,4-dienyl)decyl 3-(3-(nitrooxy)propylamino)propanoate

0.42 g (1.6 mmol) of *N*-[3-(nitrooxy)propyl]-β-alanine nitric acid salt were dissolved in 50 ml of dioxane/1N NaOH 1:2. The solution was cooled in an ice bath and Boc_2O (1.2 eq.) was added. The mixture was kept under stirring for 16 hours then was partially concentrated under reduced pressure, diluted with 50 ml of water and washed with diethyl ether (2 x 15 ml). The aqueous phase was acidified to pH 2 – 3 with 1N HCl and extracted with EtOAc (3 x 20 ml); the organic layers were unified and washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The colorless oil was readily dissolved in 15 ml of CH_2Cl_2, the solution was cooled in an ice bath and EDC·HCl (1.5 eq.) and DMAP (0.1 eq.) were added and the mixture was stirred for 1 hour; after that period idebenone (1 eq.) was added and the solution was stirred for 4 days. The solvent was removed under reduced pressure, the residue was taken up with 20 ml of CH_2Cl_2 and washed with 1N HCl (1 x 10 ml), brine, dried over Na_2SO_4 and evaporated under reduced pressure. After a partial purification by flash chromatography on silica gel (eluent: petroleum ether / EtOAc 20%) the product was dissolved in 10 ml of CH_2Cl_2 / TFA 10% and kept under stirring at r.t. for 2 hours. The solvent was then removed under reduced pressure and the residue was taken up with 20 ml of EtOAc and washed with Na_2CO_3 10% solution (2 x 10 ml), brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent CH_2Cl_2 / CH_3OH 3%) to give the title product as an orange oil (12% overall yield).

^{1}H-NMR ($CDCl_3$): δ, 4.55 (2H, t, J = 6.3 Hz, CH_2ONO_2); 4.08 (2H, t, J = 6.6 Hz, CH_2O lat. chain Id); 3.99 (6H, s, $2CH_3O$ Id); 2.89 (2H, t, J = 6.6 Hz, CH_2N); 2.75 (2H, t, J = 6.6 Hz, CH_2N); 2.51 (2H, t, J = 6.3 Hz, CH_2CO); 2.47 – 2.42 (2H, m, CH_2 lat. chain Id); 2.01 (3H, s, CH_3 Id); 1.94 – 1.85 (2H, m, $CH_2CH_2CH_2$); 1.80 (1H, s, NH); 1.80 – 1.58 (2H, m, CH_2 lat. chain Id); 1.34 – 1.29 (14H, m, $7CH_2$ lat. chain Id).

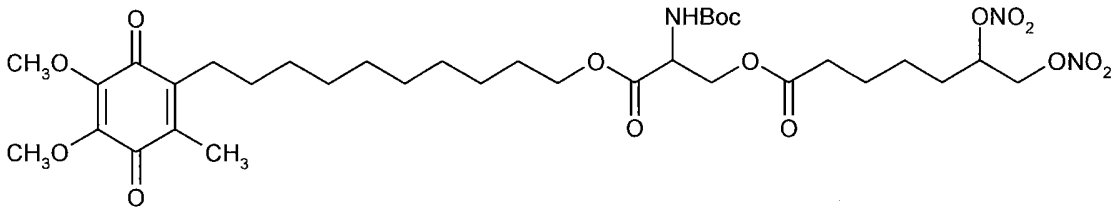
^{13}C-NMR ($CDCl_3$): δ, 184.7; 184.2; 172.8; 144.3 (two overlapping peaks); 143.0; 138.7; 71.5; 64.7; 61.1; 45.6; 44.9; 34.6; 29.8; 29.4; 29.3; 29.2; 28.7; 28.6; 27.2; 26.4; 25.9; 11.9.

MS CI (isobutane) (m/z): 513 [MH^+].

Anal. Calc. For $C_{25}H_{40}N_2O_9 \cdot 0.25\ H_2O$: C% 58.07, H% 7.89, N% 5.42; found: C% 58.01, H% 7.72, N% 5.36.

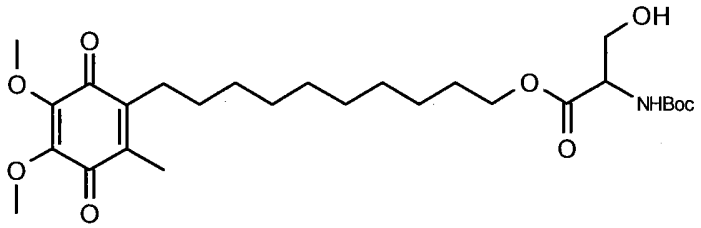
Example 7

Synthesis of [2-(tert-butoxycarbonylamino)-3-[10-(4,5-dimethoxy-2-methyl-3,6-dioxo-cyclohexa-1,4-dien-1-yl)decoxy]-3-oxo-propyl] 6-methyloctanoate (compound (7))



(7)

Step 1: Synthesis Of 10-(4,5-dimethoxy-2-methyl-3,6-dioxo-cyclohexa-1,4-dien-1-yl)decyl 2-(tert-butoxycarbonylamino)-3-hydroxy-propanoate



N-(*tert*-butoxycarbonyl)-*O*-tetrahydro-2*H*-pyran-2-yl-serine (0.09 g, 0.3 mmol) was solubilized in CH_2Cl_2; the solution was cooled in an ice bath and EDC·HCl (1.2 eq.) and DMAP (0.15 eq.) were added. After 1 hour idebenone (0.1 g, 0.3 mmol) was added

and the solution was allowed to reach r.t. and kept under stirring for 16 hours. Afterward the mixture was dried under reduced pressure and the residue was purified by flash chromatography on silica gel (eluent petroleum ether / EtOAc 20%) to afford the product as an orange oil, which was readily solubilized in CH_3OH (15 ml); 0.1 eq. of p-toluenesulfonic acid were then added and the solution was kept under stirring for 90 min. Afterward the mixture was concentrated under reduced pressure, the residue was taken up with CH_2Cl_2 (20 ml) and the solution was washed with NaOH 10% solution (2 x 10 ml), water, brine and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent petroleum ether / EtOAc 30%) to afford the title product as an orange oil (44% overall yield).

^{1}H-NMR ($CDCl_3$): δ, 5.58 – 5.60 (1H, m, NH); 4.36 - 4.35 (1H, m, CH serine); 4.17 (2H, t, J = 6.6 Hz, CH_2O lat. chain Id); 3.99 (6H, s, $2CH_3O$ Id); 3.98 – 3.96 (2H, m, CH_2O serine); 2.95 (1H, s br, OH serine); 2.45 (2H, m, CH_2 lat. chain Id); 2.02 (3H, s, CH_3 Id); 1.65 (2H, m, CH_2 lat. chain Id); 1.45 (9H, s, $3CH_3$ boc); 1.34 – 1.28 (14H, m, $7CH_2$ lat. chain Id).

^{13}C-NMR ($CDCl_3$): δ, 184.7; 184.2; 171.0; 155.8; 144.2; 144.3; 143.1; 138.7; 80.1; 65.8; 63.5; 61.2; 55.8; 29.8; 29.4 (two overlapping peaks); 29.3; 29.1; 28.7; 28.5; 28.3; 26.4; 25.8; 11.9.

MS CI (isobutane) (m/z): 525 [MH^+].

Step 2: Synthesis of 6,7-bis(nitrooxy)heptanoic acid

The title compound was prepared as described by Lazzarato, L. et al. in *J. Med. Chem.* 2008, *51*, 1894–1903.

Step 3: Synthesis of [2-(tert-butoxycarbonylamino)-3-[10-(4,5-dimethoxy-2-methyl-3,6-dioxo-cyclohexa-1,4-dien-1-yl)decoxy]-3-oxo-propyl] 6-methyloctanoate

0.14 g (0.51 mmol) of 6,7-bis(nitrooxy)heptanoic acid (obtained in Step 2) were dissolved in 15 ml of CH_2Cl_2 with few drops of DMF. The solution was cooled in an ice bath and EDC·HCl (1.5 eq.) and DMAP (0.1 eq.) were added. The solution was kept under stirring for 1 hour and then 10-(4,5-dimethoxy-2-methyl-3,6-dioxo-cyclohexa-1,4-

dien-1-yl)decyl 2-(tert-butoxycarbonylamino) -3-hydroxy-propanoate (obtained as described in Step 1) (0.27 g, 0.51 mmol) was added. The mixture was stirred at r.t. for 4 days, then was washed with water (1 x 10 ml), brine (1 x 10 ml), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether / EtOAc 25% to 30%) to afford the title product as an orange oil (0.18 g, 46%).

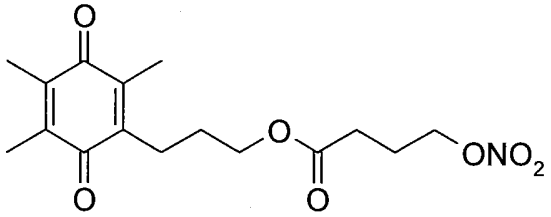
^{1}H-NMR ($CDCl_3$): δ,5.30 – 5.27 (1H, m, $CHONO_2$); 4.79 – 4.74 (1H, m, C*H'*H''ONO_2); 4.57 – 4.43 (3H, m, CH_2 serine, CH serine); 4.37 – 4.33 (1H, m, CH'*H''*ONO_2); 4.15 (2H, t, *J* = 6.6 Hz, CH_2O Id); 3.99 (6H, s, $2CH_3O$ Id); 2.47 – 2.42 (2H, m, CH_2 lat. chain Id); 2.34 (2H, t, *J* = 7.0 Hz, CH_2CO hept.); 2.01 (3H, s, CH_3 Id); 1.80 – 1.28 (31H, m, $3CH_2$ hept., $8CH_2$ lat. chain Id, $3CH_3$ boc).

^{13}C-NMR ($CDCl_3$): δ, 184.7; 184.2; 172.5; 169.8; 155.1; 144.3; 144.2; 143.0; 138.7; 80.3; 78.9; 71.1; 66.1; 64.4; 61.2; 53.0; 33.4; 29.8; 29.4 (two overlapping peaks); 29.3; 29.2; 29.0; 28.7; 28.5; 28.3; 26.4; 25.8; 24.3; 24.2; 11.3.

MS CI (isobutane) (m/z): 760 [MH^+].

Example 8

Synthesis of 3-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dien-1-yl)propyl-4-(nitrooxy)butanoate (compound (8))



(8)

Step 1: Synthesis of 1,4-Dimethoxy-2,3,5-trimethylbenzene

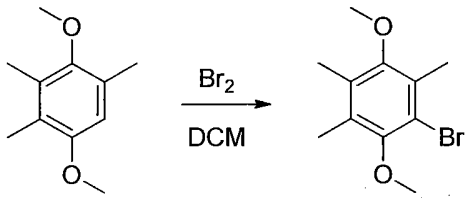
To a stirred solution of commercial trimethylhydroquinone (3.04 g, 20.0 mmol) in dry DMF (50 mL) under a nitrogen atmosphere sodium hydride (60% suspension in mineral oil, 1.76 g, 44.0 mmol) was added, and the reaction mixture was stirred at room temperature for 30 min. Afterward, iodomethane (5.0 mL, 80.0 mmol) was added, and

mixture was stirred at 40°C for 2 h. After cooling back to room temperature the reaction mixture was poured in brine (75 mL) and extracted twice with diethyl ether. The combined organic layers were dried over sodium sulphate and concentrated to dryness. Purification by silica gel flash column chromatography eluting with 80:20 v/v petroleum ether:DCM gave the product as a colorless oil (2.80 g, 78%).

TLC: R_f = 0.30 petroleum ether:DCM 80:20 v/v.

Spectroscopic data were as reported by Lipshutz, B. H et al, in *Tetrahedron* **1998**, *54*, 1241.

Step 2: Synthesis of 1-Bromo-2,5-dimethoxy-3,4,6-trimethyl benzene

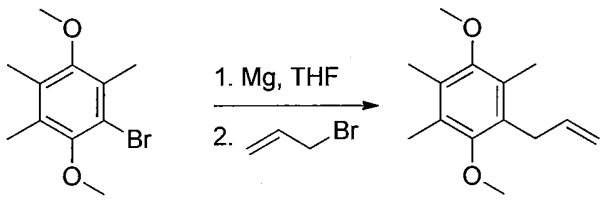


To a stirred solution of 1,4-dimethoxy-2,3,5-trimethylbenzene (obtained in Step 1) (670 mg, 3.72 mmol) in DCM (20 mL) a solution of bromine (0.20 mL, 3.91 mmol) in DCM (10 mL) was slowly added, and the resulting mixture was stirred at room temperature for 1 h. Water was added, the organic layer was separated and washed with 1 M NaOH and brine. The combined organic layers were dried over sodium sulphate and concentrated to dryness to give the product as a white solid (870 mg, 90%).

TLC: R_f = 0.20 petroleum ether:DCM 90:10 v/v

Spectroscopic data were as reported in the literature by Riering, H. et al, Chem. Ber. **1994**, *127*, 859-874.

Step 3: Synthesis of 1-Allyl-2,5-dimethoxy-3,4,6-trimethyl benzene



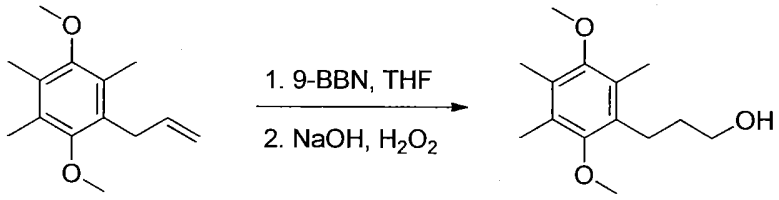
A three-neck round-bottomed flask equipped with a reflux condenser and a

dropping funnel under a nitrogen atmosphere was charged with dry THF (3 mL) and dry Mg turnings (150 mg, 6.24 mmol). Iodine (1 mg) was added, the stirred suspension was warmed to 45°C and a solution of 1-bromo-2,5-dimethoxy-3,4,6-trimethylbenzene (obtained in Step 2) (1.08 g, 4.16 mmol) in dry THF (10 mL) was added dropwise over 15 min. The reaction mixture was then stirred at 45°C for 30 min and, after cooling back to room temperature, allyl bromide (0.72 mL, 8.32 mmol) was added. The mixture was stirred at room temperature for 3 h, and a saturated NH_4Cl solution was added. The mixture was extracted with EtOAc and washed with water and brine. The combined organic layers were dried over sodium sulphate and concentrated to dryness. Purification by silica gel flash column chromatography eluting with 85:15 v/v petroleum ether:DCM gave the product as a colorless oil (650 mg, 71%).

TLC: R_f = 0.40 petroleum ether:DCM 90:10 v/v

Spectroscopic data were as reported in the literature by Riering, H. et al, Chem. Ber. **1994**, *127*, 859-874.

Step 4: Synthesis of 1,4-Dimethoxy-2-(3-hydroxypropyl)-3,5,6-trimethylbenzene



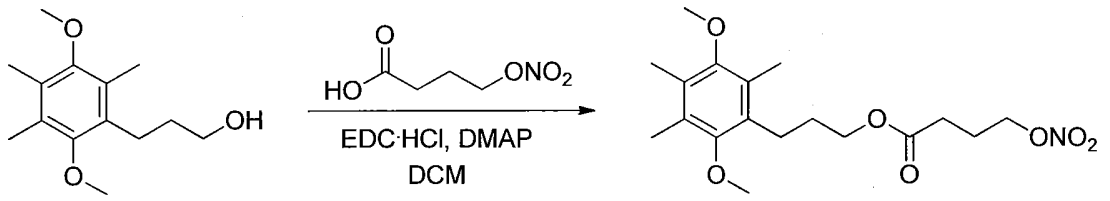
To a stirred solution of 9-BBN (0.5 M in THF, 1.85 mL, 0.92 mmol) under a nitrogen atmosphere a solution of 1-allyl-2,5-dimethoxy-3,4,6-trimethylbenzene (obtained in Step 3) (170 mg, 0.77 mmol) in dry THF (4 mL) was slowly added. The reaction mixture was stirred overnight at room temperature and was subsequently heated at reflux for further 2 h. After cooling to 0°C, an aqueous 3 M NaOH solution (1.23 mL, 3.70 mmol) was added, and the mixture was stirred for 1 h at 0°C. Hydrogen peroxide (30% in water, 1.23 mL, 3.70 mmol) was then added, and the reaction mixture was stirred at 0°C for 1 h. The mixture was then saturated with brine and extracted with THF. The combined organic layers were dried over sodium sulphate and concentrated to dryness. Purification

by silica gel flash column chromatography eluting with 85:15 v/v n-hexane:EtOAc gave the product as a colorless oil (100 mg, 55%).

TLC: R_f = 0.30 petroleum ether:EtOAc 80:20 v/v

Spectroscopic data were as reported in the literature by Riering, H. et al, Chem. Ber. 1994, *127*, 859-874.

Step 5: Synthesis of 3-(2,5-Dimethoxy-3,4,6-trimethylphenyl) propyl 4-(nitrooxy)butanoate



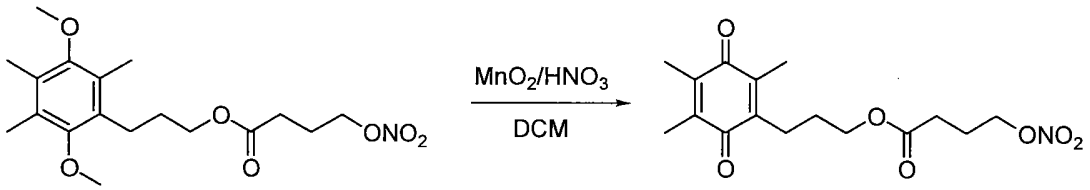
To a stirred solution of 4-(nitrooxy)butanoic acid (prepared as described by Almirante, N. et al in WO2011101245 (A1), Example 32) (125 mg, 0.84 mmol) in dry DCM (20 mL), DMAP (10 mg, 0.08 mmol) was added followed by EDC·HCl (210 mg, 1.1 mmol) and 3-(2,5-dimethoxy-3,4,6-trimethylphenyl)propan-1-ol (prepared in Step 4) (200 mg, 0.84 mmol). The reaction mixture was stirred at room temperature for 4 h. Afterward, DCM was added and the mixture was washed with water and brine. The combined organic layers were dried over sodium sulphate and concentrated to dryness. Purification by silica gel flash column chromatography eluting with 80:20 v/v petroleum ether:EtOAc gave the product as an orange oil (180 mg, 58%).TLC: R_f = 0.60 petroleum ether:EtOAc 80:20 v/v

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77-1.90 (2H, *m*), 2.07 (2H, *p*, *J* = 6.8 Hz), 2.18 (6H, *s*), 2.21 (3H, *s*), 2.47 (2H, *t*, *J* = 7.2 Hz), 2.60-2.75 (2H, *m*), 3.64 (3H, *s*), 3.66 (3H, *s*), 4.16 (2H, *t*, *J* = 6.5 Hz), 4.53 (2H, *t*, *J* = 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 12.7, 12.9, 22.3, 23.7, 29.1, 30.2, 60.1, 60.8, 64.9, 72.1, 127.2, 128.0, 128.6, 131.0, 152.9, 153.1, 172.3.

CI-MS $[M+H]^+$ *m/z* 370 (80).

Step 6: Synthesis of 3-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dien-1-yl)propyl-

4-(nitrooxy)butanoate (compound 8)



To a stirred solution of 3-(2,5-dimethoxy-3,4,6-trimethylphenyl)propyl 4-(nitrooxy)butanoate (obtained in Step 5) (150 mg, 0.41 mmol) in DCM (5 mL) at 0°C, manganese (IV) oxide (0.05 mg) and 6 M HNO_3 (0.34 mL) were added. After stirring the resulting solution at 0°C for 10 min, manganese (IV) oxide (706 mg, 8.12 mmol) followed by 6 M HNO_3 (0.67 mL, 4.02 mmol) were added, and the resulting dark suspension was stirred at room temperature overnight. Dichloromethane was added to the suspension, and the reaction mixture was then washed with water and brine. Purification by silica gel flash column chromatography eluting with 85:15 v/v petroleum ether:EtOAc gave the title compound as an orange oil (100 mg, 72%).

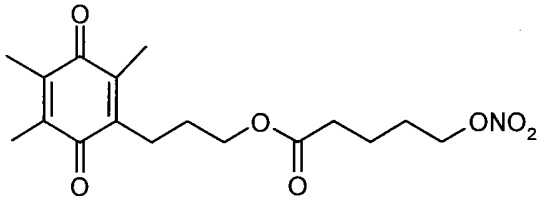
TLC: R_f = 0.20 petroleum ether:EtOAc 85:15 v/v

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71-1.84 (2H, *m*), 2.02 (6H, *s*), 2.04 (3H, *s*), 2.05-2.18 (2H, *m*), 2.48 (2H, *t*, *J* = 7.2 Hz), 2.54-2.61 (2H, *m*), 4.12 (2H, *t*, *J* = 6.3 Hz), 4.55 (2H, *t*, *J* = 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 12.3, 12.4, 22.3, 23.2, 27.6, 30.1, 64.3, 72.1, 140.5, 140.6, 140.8, 143.0, 172.2, 186.9, 187.5.

CI-MS $[M+H]^+$ *m/z* 340 (100).

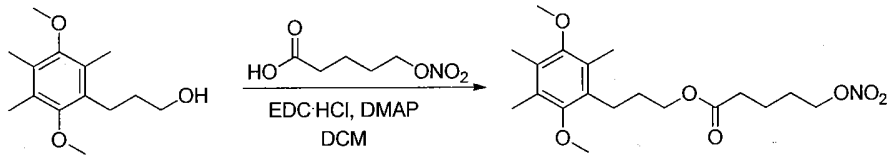
Example 9

Synthesis of 3-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dien-1-yl)propyl 5-(nitrooxy)pentanoate (compound (9))



(9)

Step 1: Synthesis of 3-(2,5-Dimethoxy-3,4,6-trimethylphenyl)propyl 5-(nitrooxy)pentanoate



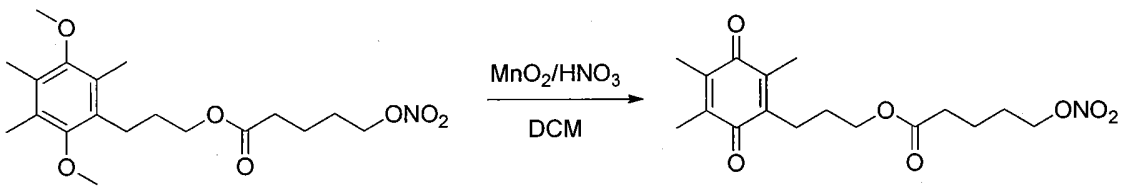
To a stirred solution of 3-(2,5-dimethoxy-3,4,6-trimethylphenyl)propan-1-ol (obtained as described in Example 8, Step 4) (70 mg, 0.29 mmol) in dry DCM (5 mL), were added 5-(nitrooxy)pentanoic acid (obtained as described by Lundy, K. M. et al, in US 2001/0012851 Al (Pub. Date: Aug. 9, 2001))(50 mg, 0.29 mmol), EDC·HCl (72 mg, 0.38 mmol) and DMAP (4 mg, 0.03 mmol). Afterward, DCM was added and the mixture was washed with water and brine. The combined organic layers were dried over sodium sulphate and concentrated to dryness. Purification by silica gel flash column chromatography eluting with 85:15 v/v n-hexane:EtOAc gave the product as an orange oil (70 mg, 63%).

TLC: R_f = 0.60 petroleum ether:EtOAc 80:20 v/v

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72-1.90 (6H, *m*), 2.18 (6H, *s*), 2.22 (3H, *s*), 2.38 (2H, *t*, *J* = 6.8 Hz), 2.61-2.74 (2H, *m*), 3.64 (3H, *s*), 3.66 (3H, *s*), 4.15 (2H, *t*, *J* = 6.5 Hz), 4.47 (2H, *t*, *J* = 5.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 12.7, 12.9, 21.2, 23.7, 26.3, 29.1 33.6, 60.1, 60.8, 64.6, 72.8, 127.2, 128.0, 128.6, 131.1, 152.9, 153.1, 172.9.

CI-MS $[M+H]^+$ *m/z* 384 (70).

Step 2: Synthesis of 3-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dien-1-yl)propyl 5-(nitrooxy)pentanoate



To a stirred solution of 3-(2,5-dimethoxy-3,4,6-trimethylphenyl)propyl 5-(nitrooxy)pentanoate (obtained in Step 1)(230 mg, 0.60 mmol) in DCM (10 mL) at 0°C,

manganese (IV) oxide (0.05 mg) and 6 M HNO_3 (0.60 mL) were added. After stirring the resulting solution at 0°C for 10 min, manganese (IV) oxide (1.04 g, 12.00 mmol) followed by 6 M HNO_3 (1.20 mL, 7.20 mmol) were added, and the resulting dark suspension was stirred at room temperature overnight. Dichloromethane was added to the suspension, and the reaction mixture was then washed with water and brine. Purification by silica gel flash column chromatography eluting with 90:10 v/v petroleum ether:EtOAc gave the product as an orange oil (100 mg, 47%).

TLC: R_f = 0.20 petroleum ether:EtOAc 90:10 v/v

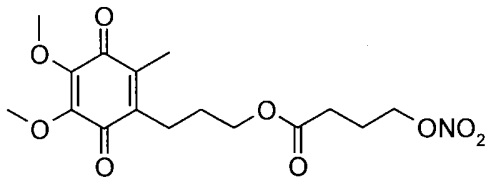
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70-1.86 (6H, *m*), 2.02 (6H, *s*), 2.03 (3H, *s*), 2.39 (2H, *t*, *J* = 6.8 Hz), 2.51-2.62 (2H, *m*), 4.10 (2H, *t*, *J* = 6.3 Hz), 4.49 (2H, *t*, *J* = 6.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 12.3, 12.4, 21.1, 23.2, 26.2, 27.6, 33.5, 64.0, 72.8, 140.5, 140.6, 140.8, 143.0, 172.8, 186.9, 187.5.

CI-MS $[M+H]^+$ *m/z* 354 (100).

Example 10

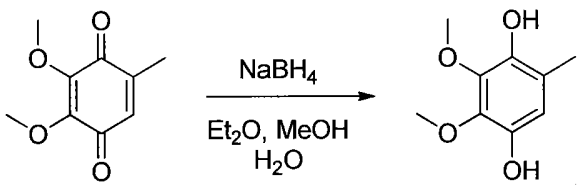
Synthesis of 3-(4,5-Dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)propyl 4-(nitrooxy)butanoate (compound (10))



(10)

Method A

Step 1a: Synthesis of 2,3-Dimethoxy-5-methylhydroquinone



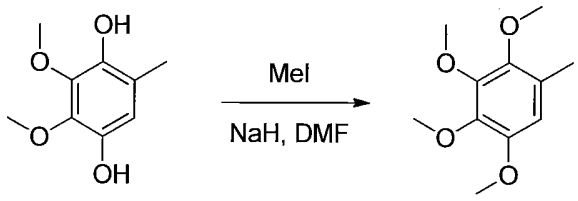
To a stirred solution of $NaBH_4$ (1.04 g, 27.5 mmol) in water (30 mL), a solution of

commercial 2,3-dimethoxy-5-methylbenzoquinone (1.00 g, 5.50 mmol) in diethyl ether (15 mL) and methanol (8 mL) was added dropwise. Afterward, the reaction mixture was extracted with diethyl ether and washed with brine. The combined organic layers were dried over sodium sulphate and concentrated to dryness to give the product as a pale yellow solid (950 mg, 88%).

TLC: R_f = 0.20 petroleum ether:EtOAc 90:10 v/v

Spectroscopic data were as reported in the literature by Daquino, C. et al, *J. Org. Chem.* **2008**, *73*, 9270

Step 2a: Synthesis of 1,2,3,4-tetramethoxy-5-methylbenzene

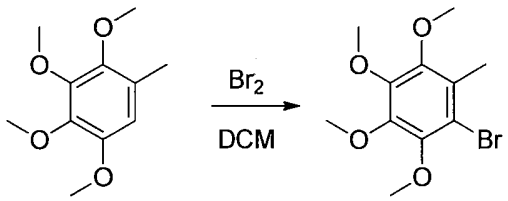


To a stirred solution of 2,3-dimethoxy-5-methylhydroquinone (obtained in Step 1a) (950 mg, 5.16 mmol) in dry DMF (20 mL) under a nitrogen atmosphere, sodium hydride (60% suspension in mineral oil, 454 mg, 11.3 mmol) was added in small portions, and the reaction mixture was stirred at room temperature for 30 min. Afterward, iodomethane (1.30 mL, 20.6 mmol) was added, and mixture was stirred at 40°C for 2 h. After cooling to room temperature the reaction mixture was poured in brine (75 mL) and extracted twice with diethyl ether. The combined organic layers were dried over sodium sulphate and concentrated to dryness. Purification by silica gel flash column chromatography eluting with 60:40 v/v petroleum ether:DCM gave the product as a colorless oil (876 mg, 80%).

TLC: R_f = 0.80 petroleum ether:EtOAc 80:20 v/v

Spectroscopic data were as those reported in the literature by Yamakoshi, H. et al, in *J. Am. Chem. Soc.* **2012**, *134*, 20681-20689.

Step 3a: Synthesis of 1-Bromo-2,3,4,5-tetramethoxy-6-methyl benzene



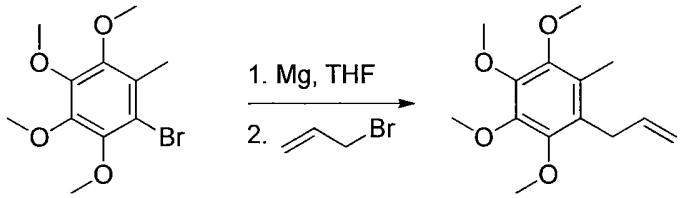
To a stirred solution of 1,2,3,4-tetramethoxy-5-methylbenzene (obtained in Step 2a) (1.60 g, 7.54 mmol) in DCM (50 mL), a solution of bromine (0.41 mL, 7.92 mmol) in DCM (15 mL) was slowly added, and the resulting mixture was stirred at room temperature for 1 h. Water was added, the organic layer was separated and washed with 1 M NaOH and brine. The combined organic layers were dried over sodium sulphate and concentrated to dryness to give the product as yellow oil (2.00 g, 91%).

Yield: 91%

TLC: R_f = 0.80 petroleum ether:EtOAc 90:10 v/v

Spectroscopic data were as those reported in the literature by Tremblay, M. S. et al, *Org. Lett.* **2005**, 7, 2417

Step 4: Synthesis of 1-Allyl-2,3,4,5-tetramethoxy-6-methyl benzene



A three-neck round-bottomed flask equipped with a reflux condenser and a dropping funnel under a nitrogen atmosphere was charged with dry THF (5 mL) and dry Mg turnings (250 mg, 10.3 mmol). Iodine (1 mg) was added, the stirred suspension was warmed to 45°C and a solution of 1-bromo-2,3,4,5-tetramethoxy-6-methylbenzene (obtained in Step 3a) (2.00 g, 6.87 mmol) in dry THF (15 mL) was added dropwise over 15 min. The reaction mixture was then stirred at 45°C for 30 min and, after cooling back to room temperature, allyl bromide (1.20 mL, 13.7 mmol) was added. The mixture was stirred at room temperature for 3 h, and a saturated NH_4Cl solution was added. The

mixture was extracted with EtOAc and washed with water and brine. The combined organic layers were dried over sodium sulphate and concentrated to dryness. Purification by silica gel flash column chromatography eluting with 50:50 v/v petroleum ether:DCM gave the product as a colorless oil (1.17 g, 68%).

TLC: R_f = 0.80 petroleum ether:EtOAc 90:10 v/v

Spectroscopic data were as those reported in the literature by Duveaua, D. Y. et al, in *Bioorg. Med. Chem.* 2010, *18*, 6429.

Alternatively 1-allyl-2,3,4,5-tetramethoxy-6-methyl benzene can be prepared in 4 steps following the procedure described in Method B.

Method B

Step 1b: Synthesis of 4,5-dimethoxy-2-methyltricyclo[6.2.1.02,7] undeca-4,9-diene-3,6-dione

To a solution of 2,3-dimethoxy-5-methyl-p-benzoquinone (4.0 g, 21.96 mmol) in glacial acetic acid (100 mL), freshly distilled cyclopentadiene (2.8 mL, 32.94 mmol, 1.5 eq) was added and the reaction was stirred overnight at r.t. The reaction was cooled to 0°C and ice/water was added. The aqueous layer was neutralized using 3M aq NaOH and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water, brine, dried on Na_2SO_4, filtered and evaporated affording the title compound (5.4 g, yield: 98%) as a dark red oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (dd, *J* = 5.6, 2.9, 1H), 6.01 (dd, *J* = 5.6, 2.8, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.42 (s, 1H), 3.08 (s, 1H), 2.83 (d, *J* = 3.9, 1H), 2.07 (d, *J* = 12.6, 3H), 1.71 – 1.62 (m, 1H), 1.54 (dt, *J* = 9.2, 1.6, 1H).

Step 2b: Synthesis of 2-allyl-4,5-dimethoxy-7-methyltricyclo [6.2.1.02,7]-undeca-4,9-diene-3,6-dione

To a stirred solution of crude 4,5-dimethoxy-2-methyltricyclo[6.2.1.02,7]undeca-4,9-diene-3,6-dione (5.4 g) in dry THF (100 mL) cooled to 0°C, potassium tert-butoxide (4.0 g, 32.9 mmol, 1.5 eq) was added portionwise. The reaction became dark reddish and was stirred at this temperature for another 30 mins then a solution of allyl bromide (2.9

mL, 35.1 mmol, 1.6 eq) in dry THF (30 mL) was added slowly. The reaction was stirred for 2h before addition of water (30 mL). The aqueous layer was acidified to pH 2 and the solution was extracted with Et2O (3 x 50 mL). The combined organic layers were washed with water and brine, dried on sodium sulfate, filtered and evaporated. The residue was purified by flash chromatography (Biotage instrument, SNAP 340 column, EtOAc in n-Hexane from 20% to 40% in 10 CV) affording the title compound as pale yellow oil (4.22 g, yield: 67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (d, J = 6.1, 2H), 5.90 – 5.69 (m, 1H), 5.10 (s, 1H), 5.05 (dd, J = 3.6, 2.1, 1H), 3.94 – 3.87 (m, 5H), 3.12 (d, J = 1.6, 1H), 3.05 – 2.99 (m, 1H), 2.70 (dd, J = 14.5, 7.6, 1H), 2.56 (dd, J = 14.5, 6.7, 1H), 1.76 (m, 1H), 1.50 (s, 3H), 1.49 (s, 1H).

Step 3b: Synthesis of 2-Allyl-3-methyl-5,6-dimethoxy-1,4-benzoquinone

A solution of 2-allyl-4,5-dimethoxy-7-methyltricyclo[6.2.1.02,7] -undeca-4,9-diene-3,6-dione (4.1 g, 14.22 mmol) in toluene (50 mL) was heated at reflux for 7 h. The reaction was then cooled down and the solvent evaporated. The residue was purified by flash chromatography (Biotage instrument, SNAP 340 column, EtOAc in n-Hexane from 20% to 40% in 10 CV) affording the title compound as red oil (4.22 g, yield: 67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 – 5.65 (m, 1H), 5.07 (dd, J = 3.9, 1.5, 1H), 5.02 (dd, J = 3.6, 1.6, 1H), 3.99 (d, J = 1.1, 5H), 3.23 (t, J = 6.7, 2H), 2.08 – 1.96 (m, 3H).

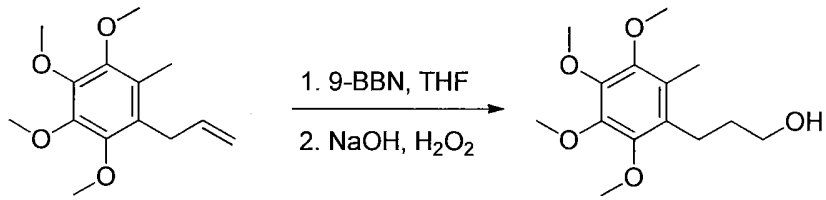
Step 4b: Synthesis of 1-Allyl-2,3,4,5-tetramethoxy-6-methyl benzene

To a stirred solution of 2-Allyl-3-methyl-5,6-dimethoxy-1,4-benzoquinone (27 g, 121.5 mmol) and tetrabutylammonium bromide (2.0 g) in THF/water (1/1, 700 mL each), sodium dithionite (211g, 1.215 mole, 10 eq) was added. The reaction was stirred for 30 min then cooled to 0°C and NaOH (73 g, 15 eq). After 30 min of stirring, methyl iodide (100 mL, 1.215 mole, 10 eq) was added and the reaction heated overnight at 40°C. The reaction was diluted with water (1 L) and extracted 3 times with Et2O (500 mL each). The combined organic layers were washed with water and brine, dried on sodium sulfate, filtered and evaporated. The residue was purified by flash chromatography (Biotage SP4,

3 SNAP 340 columns, EtOAc in n-Hexane from 5% to 20% in 10 CV) affording the title compound as colourless oil (19.7 g, yield: 64%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (ddt, J = 16.0, 10.2, 5.8, 1H), 5.04 – 4.97 (m, 1H), 4.92 (dq, J = 17.1, 1.8, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.38 (dt, J = 5.8, 1.8, 2H), 2.18 (s, 3H).

Step 5b: synthesis of 1-(3-Hydroxypropyl)-2,3,4,5-tetramethoxy-6-methylbenzene

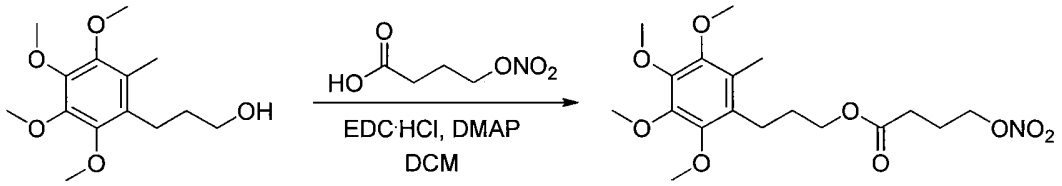


To a stirred solution of 9-BBN (0.5 M in THF, 11.2 mL, 5.57 mmol) under a nitrogen atmosphere, a solution of 1-allyl-2,3,4,5-tetramethoxy-6-methylbenzene (obtained as described in Step 4a or 4b) (1.17 g, 4.64 mmol) in dry THF (10 mL) was slowly added. The reaction mixture was stirred overnight at room temperature and was subsequently heated at reflux for further 2 h. After cooling to 0°C, an aqueous 3 M NaOH solution (7.40 mL, 22.2 mmol) was added, and the mixture was stirred for 1 h at 0°C. Hydrogen peroxide (30% in water, 7.40 mL, 22.2 mmol) was then added, and the reaction mixture was stirred at 0°C for 1 h. The mixture was then saturated with brine and extracted with THF. The combined organic layers were dried over sodium sulphate and concentrated to dryness. Purification by silica gel flash column chromatography eluting with 80:20 v/v petroleum ether:EtOAc gave the product as a colorless oil (550 mg, 44%).

TLC: R_f = 0.20 petroleum ether:EtOAc 80:20 v/v

Spectroscopic data were as those reported in the literature by Duveaua, D. Y. et al, in *Bioorg. Med. Chem.* **2010**, *18*, 6429.

Step 6b: Synthesis of 3-(2,3,4,5-Tetramethoxy-6-methylphenyl) propyl 4-(nitrooxy)butanoate



To a stirred solution of 3-(2,3,4,5-tetramethoxy-6-methylphenyl)propan-1-ol (obtained in Step 5b) (220 mg, 0.81 mmol) in dry DCM (10 mL), 4-(nitrooxy)butanoic acid ((prepared as described by Almirante, N. et al in WO2011101245 (A1), Example 32) 121 mg, 0.81 mmol) followed by DMAP (10 mg, 0.08 mmol) and EDC·HCl (202 mg, 1.05 mmol) were added. The reaction mixture was stirred at room temperature for 4 h. Afterward, DCM was added and the mixture was washed with water and brine. The combined organic layers were dried over sodium sulphate and concentrated to dryness. Purification by silica gel flash column chromatography eluting with 85:15 v/v petroleum ether:EtOAc gave the product as a red oil (180 mg, 61%).

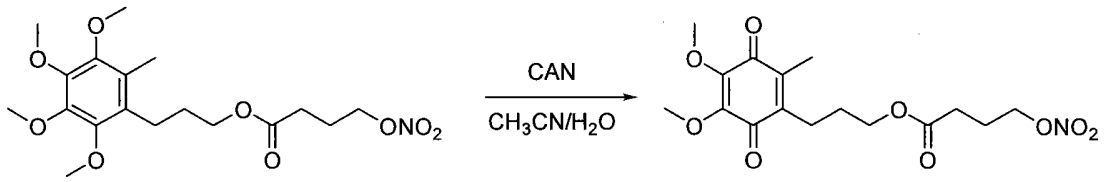
TLC: R_f = 0.70 petroleum ether:EtOAc 80:20 v/v

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74-1.87 (2H, *m*), 2.02-2.13 (2H, *m*), 2.16 (3H, *s*), 2.48 (2H, *t*, *J* = 7.1 Hz), 2.60-2.69 (2H, *m*), 3.78 (3H, *s*), 3.82 (3H, *s*), 3.89 (3H, *s*), 3.91 (3H, *s*), 4.14 (2H, *t*, *J* = 6.5 Hz), 4.53 (2H, *t*, *J* = 6.3 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 22.3, 23.3, 28.9, 30.2, 60.7, 61.0 (2C), 61.1, 64.8, 72.0, 124.9, 128.4, 144.6, 145.2, 147.8 (2C), 172.3.

CI-MS $[M+H]^+$ *m/z* 402 (35).

Step 7: Synthesis of 3-(4,5-Dimethoxy-2-methyl-3,6-dioxocyclo hexa-1,4-dien-1-yl)propyl 4-(nitrooxy)butanoate (compound (10))



To a stirred solution of 3-(2,3,4,5-tetramethoxy-6-methylphenyl)propyl

4-(nitrooxy)butanoate (220 mg, 0.55 mmol) in CH_3CN/water (50:50 v/v, 15 mL) at 0°C, a solution of ceric ammonium nitrate (603 mg, 1.10 mmol) in CH_3CN/water (50:50 v/v, 15 mL) was added dropwise. The resulting solution was stirred at 0°C for 30 min, and the reaction mixture was then extracted twice with DCM. The combined organic layers were dried over sodium sulphate and concentrated to dryness. Purification by silica gel flash column chromatography eluting with 80:20 v/v petroleum ether:EtOAc gave the product as a red oil (90 mg, 44%).

TLC: R_f = 0.30 petroleum ether:EtOAc 80:20 v/v

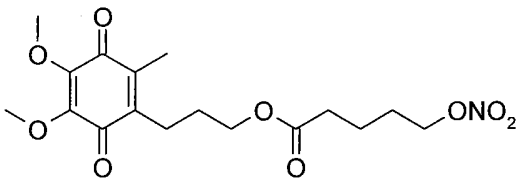
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71-1.83 (2H, *m*), 2.03 (3H, *s*), 2.05-2.14 (2H, *m*), 2.48 (2H, *t*, *J* = 7.1 Hz), 2.52-2.59 (2H, *m*), 4.00 (6H, *s*), 4.12 (2H, *t*, *J* = 6.3 Hz), 4.54 (2H, *t*, *J* = 6.3 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 22.2, 23.0, 27.5, 30.1, 61.2, 64.1, 72.1, 139.4, 141.5, 144.3, 144.4, 172.2, 183.9, 184.4.

CI-MS $[M+H]^+$ *m/z* 372 (50).

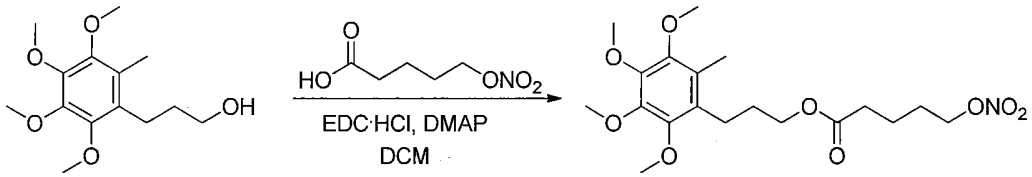
Example 11

Synthesis of: 3-(4,5-Dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)propyl 5-(nitrooxy)pentanoate (compound (11))



(11)

Step 1: Synthesis of 3-(2,3,4,5-tetramethoxy-6-methylphenyl) propyl 5-(nitrooxy)pentanoate



To a stirred solution of 3-(2,3,4,5-tetramethoxy-6-methylphenyl)propan-1-ol

(obtained in Example 10, Step 5) (240 mg, 0.89 mmol) in dry DCM (10 mL), 5-(nitrooxy)pentanoic acid (obtained in Example 9, Step 1) (145 mg, 0.89 mmol) was added followed by DMAP (11 mg, 0.09 mmol) and EDC·HCl (222 mg, 1.16 mmol). The reaction mixture was stirred at room temperature for 4 h. Afterward, DCM was added and the mixture was washed with water and brine. The combined organic layers were dried over sodium sulphate and concentrated to dryness. Purification by silica gel flash column chromatography eluting with 80:20 v/v petroleum ether:EtOAc gave the product as a red oil (180 mg, 49%).

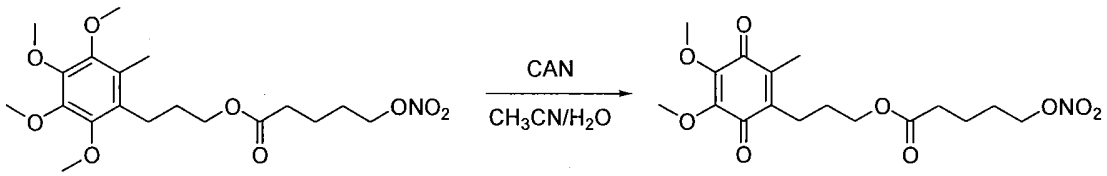
TLC: R_f = 0.70 petroleum ether:EtOAc 80:20 v/v

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72-1.91 (6H, *m*), 2.17 (3H, *s*), 2.40 (2H, *t*, *J* = 6.7 Hz), 2.61-2.69 (2H, *m*), 3.80 (3H, *s*), 3.84 (3H, *s*), 3.90 (3H, *s*), 3.92 (3H, *s*), 4.15 (2H, *t*, *J* = 6.5 Hz), 4.49 (2H, *t*, *J* = 5.7 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 21.2, 23.4, 26.3, 29.1, 33.6, 60.7, 61.1 (2C), 61.2, 64.6, 72.8, 125.0, 128.6, 144.7, 145.2, 147.8, 147.9, 173.0.

CI-MS $[M+H]^+$ *m/z* 416 (10).

Step 2: Synthesis of 3-(4,5-Dimethoxy-2-methyl-3,6-dioxocyclo hexa-1,4-dien-1-yl)propyl 5-(nitrooxy)pentanoate (compound (11))



To a stirred solution of 3-(2,3,4,5-Tetramethoxy-6-methylphenyl)propyl 5-(nitrooxy)pentanoate (obtained in Step 1) (165 mg, 0.40 mmol) in CH_3CN/water (50:50 v/v, 15 mL) at 0°C, a solution of ceric ammonium nitrate (440 mg, 0.80 mmol) in CH_3CN/water (50:50 v/v, 15 mL) was added dropwise. The resulting solution was stirred at 0°C for 2 h, and the reaction mixture was then extracted twice with DCM. The combined organic layers were dried over sodium sulphate and concentrated to dryness. Purification by silica gel flash column chromatography eluting with 75:25 v/v petroleum

ether:EtOAc gave the product as a red oil (80 mg, 52%).

TLC: R_f = 0.10 petroleum ether:EtOAc 80:20 v/v

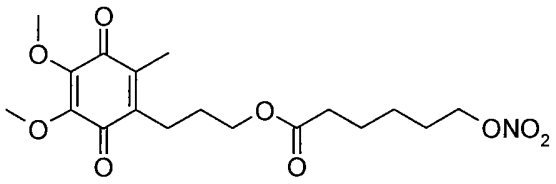
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66-190 (6H, *m*), 2.21 (3H, *s*), 2.30-2.46 (2H, *m*), 2.60-2.74 (2H, *m*), 3.64 (3H, *s*), 3.66 (3H, *s*), 4.05-4.23 (2H, *m*), 4.39-4.56 (2H, *m*).

^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 21.1, 23.0, 26.2, 27.6, 33.5, 61.2, 63.9, 72.8, 139.4, 141.6, 144.4, 172.8, 183.9, 184.4.

CI-MS $[M+H]^+$ *m/z* 386 (45).

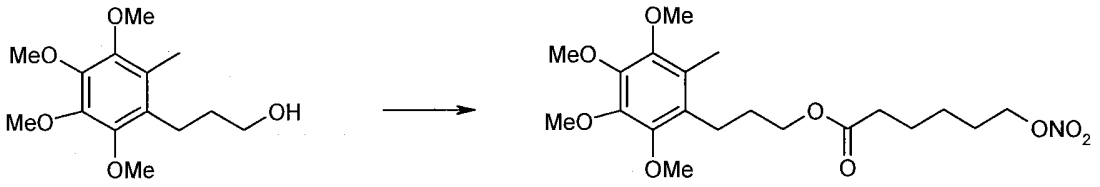
Example 12

Synthesis of 3-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)propyl 6-(nitrooxy)hexanoate (compound (12))



(12)

Step 1: Synthesis of 3-(2,3,4,5-tetramethoxy-6-methylphenyl) propyl 6-(nitrooxy)hexanoate



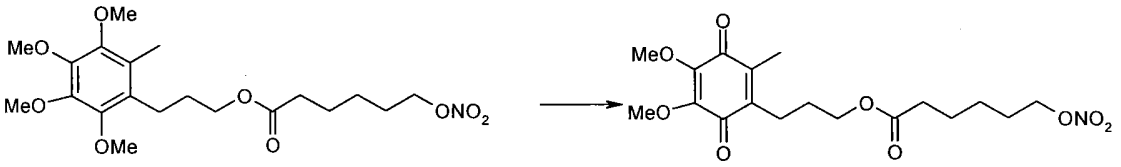
To a stirred solution of 3-(2,3,4,5-tetramethoxy-6-methylphenyl)propan-1-ol (obtained in Example 10, Step 5) (400 mg, 1.48 mmol) in dry DCM (20 mL), 6-(nitrooxy)hexanoic acid (prepared as described by Ronsin, G. et al. in WO2013/060673 A1) 262 mg, 1.48 mmol) was added followed by DMAP (20 mg, 0.15 mmol) and EDC·HCl (370 mg, 1.92 mmol). The reaction mixture was stirred at room temperature for 4 h. Afterward, DCM was added and the mixture was washed with water and brine. The combined organic layers were dried over sodium sulphate and concentrated to dryness. to give the product

as a pale yellow oil (420 mg, 66%).

TLC: R_f = 0.63 petroleum ether:EtOAc 80:20 v/v

CI-MS $[M+H]^+$ m/z 430 (60).

Step 2: Synthesis of 3-(4,5-Dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)propyl 6-(nitrooxy)hexanoate (corresponding to compound (12)



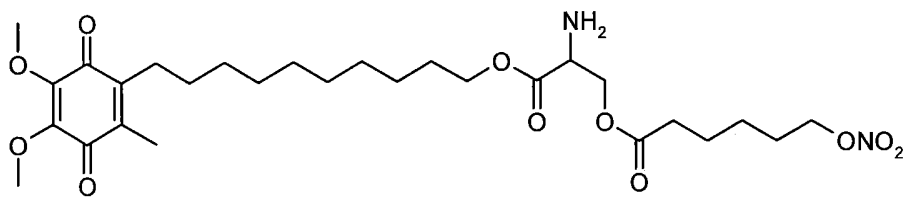
To a stirred solution of 3-(2,3,4,5-Tetramethoxy-6-methylphenyl)propyl 6-(nitrooxy)hexanoate (obtained in Step 1) (420 mg, 0.98 mmol) in CH_3CN/water (50:50 v/v, 25 mL) at 0°C, a solution of ceric ammonium nitrate (1.075 g, 1.96 mmol) in CH_3CN/water (50:50 v/v, 25 mL) was added dropwise. The resulting solution was stirred at 0°C for 2 h, and the reaction mixture was then extracted twice with DCM. The combined organic layers were dried over sodium sulphate and concentrated to dryness. Purification by silica gel flash column chromatography eluting with 80:20 v/v petroleum ether:EtOAc gave the product as a red oil (250 mg, 64%).

TLC: R_f = 0.20 petroleum ether:EtOAc 80:20 v/v

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40-1.51 (2H, m), 1.63-1.81 (6H, m), 2.03 (3H, s), 2.35 (2H, t, J = 6.0 Hz), 2.55 (2H, t, J = 9.0 Hz), 4.00 (6H, s), 4.09 (2H, t, J = 9.0 Hz), 4.46 (2H, t, J = 6.0 Hz).

Example 13

Synthesis of [2-amino-3-[10-(4,5-dimethoxy-2-methyl-3,6-dioxo-cyclohexa-1,4-dien-1-yl)decoxy]-3-oxo-propyl] heptanoate (Compound (13))



(13)

0.15 g (0.2 mmol) of [2-(tert-butoxycarbonylamino)-3-[10-(4,5-dimethoxy-2-methyl-3,6-dioxo-cyclohexa-1,4-dien-1-yl)decoxy]-3-oxo-propyl] heptanoate (Compound 5, prepared in Example 5) were solubilized in 10 ml of CH_2Cl_2 / TFA 10%. The solution was kept under stirring at r.t. for 8 hours, then it was evaporated under reduced pressure; the residue was taken up with 15 ml of EtOAc and washed with 1N NaOH solution (3 x 10 ml), brine, dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure to afford the title product as orange oil (0.11 g, 87%).

^{1}H-NMR (CD_3OD): δ, 4.50 – 4.46 (3H, m, CH serine, CH_2ONO_2); 4.16 – 4.11 (2H, m, CH_2O lat. chain Id); 3.95 (6H, s, $2CH_3O$ Id); 3.91 – 3.77 (2H, m, CH_2 serine); 2.47 – 2.43 (2H, m, CH_2 lat. chain Id); 2.32 – 2.27 (2H, m, CH_2CO); 1.99 (3H, s, CH_3 Id); 1.75 – 1.60 (5H, m, CH_2 hept, 3H lat. chain Id); 1.43 – 1.32 (19H, m, $3CH_2$ hept, 13H lat. chain Id).

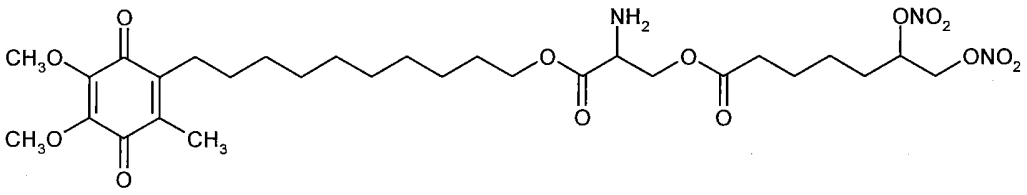
^{13}C-NMR (CD_3OD): δ, 185.0; 184.5; 175.2; 171.0; 144.8; 144.7; 143.1; 139.0; 73.4; 65.3; 61.7; 60.4; 55.1; 35.4; 29.6; 29.4; 29.3; 29.2 (two overlapping peaks); 28.5 (two overlapping peaks); 26.5; 26.0; 25.7; 25.4; 25.3; 10.8.

MS CI (isobutane) (m/z): 599 [MH^+].

Anal. Calc. For $C_{29}H_{46}N_2O_{11}$: C% 58.18, H% 7.74, N% 4.68; found: C% 58.07, H% 7.91, N% 4.51.

Example 14

Synthesis of 2-amino-3-(10-(4,5-dimethoxy-2-methyl-3,6-dioxo-cyclohexa-1,4-dienyl)decyloxy)-3-oxopropyl 6,7-bis(nitrooxy) heptanoate (compound (14))



(14)

0.05 g (0.06 mmol) of [2-(tert-butoxycarbonylamino)-3-[10-(4,5-dimethoxy-2-methyl-3,6-dioxo-cyclohexa-1,4-dien-1-yl)decoxy]-3-oxo-propyl] 6-methyloctanoate

(Compound (7) obtained in Example 7) were solubilized in 5 ml of CH_2Cl_2 / TFA 10%. The solution was kept under stirring at r.t. for 8 hours, then it was evaporated under reduced pressure; the residue was taken up with 15 ml of EtOAc and washed with $NaHCO_3$ saturated solution (3 x 10 ml), brine, dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (eluent: CH_2Cl_2 / CH_3OH 2%) to afford the title product as orange oil (0.02 g, 50%).

^{1}H-NMR ($CDCl_3$): δ,5.31 – 5.28 (1H, m, $CHONO_2$); 4.79 – 4.73 (1H, m, C*H*'H''ONO_2); 4.68 – 4.64 (1H, m, CHN serine); 4.52 – 4.45 (1H, m, CH'*H*''ONO_2); 4.18 (2H, t, *J* = 6.8 Hz, CH_2O lat. chain Id); 4.02 – 3.94 (8H, m, CH_2O serine, $2CH_3O$ Id); 2.47 – 2.42 (2H, m, CH_2 lat. chain Id); 2.31 (2H, t, *J* = 7.0 Hz, CH_2CO hept.); 2.01 (3H, s, CH_3 Id); 1.82 – 1.28 (22H, m, $8CH_2$ Id, $3CH_2$ hept.).

^{13}C-NMR ($CDCl_3$): δ, 184.7; 184.2; 172.8; 170.5; 144.3 (two overlapping peaks); 143.1; 138.7; 79.0; 71.2; 66.1; 63.6; 61.2; 54.7; 35.7; 29.7; 29.4; 29.3; 29.1; 29.0 (two overlapping peaks); 28.7; 28.5; 26.4; 25.7; 24.8; 24.4; 11.9.

MS CI (isobutane) (m/z): 660 [MH^+].

Anal. Calc. For $C_{29}H_{45}N_3O_{14}$ C% 52.89, H% 6.88, N% 6.37. Found C% 52.66, H% 6.92, N%6.08.

Example 15

TBARS test: In vitro Antioxidant activity

The antioxidant properties of compound of the invention and of reference antioxidant compounds were assessed in an in vitro test.

Tested compounds: (1), (2), (3), (4), (8), (9) and (14).

Reference antioxidant compounds: ferulic, caffeic acids, edavarone, melatonin and idebenone.

The antioxidant properties of the tested compounds were assessed after NADPH-induced lipidic peroxidation of membrane lipids in rat hepatocytes using the detection of 2-thiobarbituric acid reactive substances (TBARS) by visible spectroscopy.

Hepatic microsomal membranes from male Wistar rats (200-250 g) were prepared by differential centrifugation (8000g, 20 min; 120000g, 1 h) in a HEPES/sucrose buffer (10 mM, 250 mM, pH 7.4) and stored at -80°C. Incubation was performed at 37°C in a Tris-HCl/KCl (100 mM/150 mM, pH 7.4) containing microsomal membranes (2 mg prot/mL), sodium ascorbate (100 μM), and DMSO solutions of the tested compounds. Lipid peroxidation was initiated by adding ADP-FeCl3 and NADPH (Method A) or 2.5 μM FeSO4 (Method B) (as described by Boschi D. et al., J. Med. Chem. 2006, 49:2886-2897).

Aliquots were taken from the incubation mixture at 5, 15, and 30 min and treated with trichloroacetic acid (TCA) 10% w/v. Lipid peroxidation was assessed by spectrophotometric (543 nm) determination of the TBARS consisting mainly of malondialdehyde (MDA). TBARS concentrations (expressed in nmol/mg protein) were obtained by interpolation with a MDA standard curve. The antioxidant activity of tested compounds was evaluated as the percent inhibition of TBARS production with respect to control samples, using the values obtained after 30 min of incubation. IC_{50} values were calculated by nonlinear regression analysis.

The results reported in Table 1 are expressed as IC_{50} of inhibition of TBARS production after 30 min incubation at 37°C and they show that the compounds of the invention inhibit the generation of TBARS with a potency that is superior to those of the reference antioxidant compounds.

Table 1: In vitro Antioxidant activity (TBARS test)

Compound	Antioxidant activity IC_{50} μM (CL 95%)	Method
Compound (1)	2.7 (2.2 - 3.2)	A
Compound (2)	1.1 (0.8 - 1.5)	A
Compound (3)	5.7 (3.7 - 8.9)	A
Compound (4)	2.8 (1.6 - 4.6)	A
Compound (8)	3.1 (2.8 - 3.6)	A

(continued)

Compound (9)	3.7 (3.2-4.3)	A
Compound (14)	2.4 (1.6 – 3.6)	A
Ferulic acid	50.5 ± 0.4 [a]	B
Caffeic acid	33 (32-34)	B
Edavarone	17 (15-18) [b]	B
Melatonin	476 (442–512) [c]	B
Idebenone	1.6 (1.2 - 2.0)	A

[a] tested at 1mM concentration;

[b] Chegaev, K. et al. J. Med. Chem. 2009, 52:574–578:

[c] Chegaev, K. et al. J. Pineal Res. 2007, 42:371–385

Example 16

Vasodilating activity

The vasodilating activities of compounds (2) and compound (4) were evaluated in an in vitro test performed on rat aortic rings.

The purposes and the protocols of this study have been approved by the Ministero della Salute, Rome, Italy.

Thoracic aortas were isolated from male Wistar rats weighing 180-200 g.

The endothelium was removed and the vessels were helically cut: three strips were obtained from each aorta. The tissues were mounted under 1.0 g tension in organ baths containing 30 ml of Krebs-bicarbonate buffer with the following composition (mM): NaCl 111.2, KCl 5.0, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.0, $NaHCO_3$ 12.0, glucose 11.1, maintained at 37°C and gassed with 95% O_2 - 5% CO_2 (pH = 7.4).

The aortic strips were allowed to equilibrate for 120 min and then contracted with 1 μM L-phenylephrine. When the response to L-phenylephrine reached a plateau, cumulative concentrations of the tested compounds were added. Results are expressed as EC_{50} ± SE (μM).

The effects of 1 μM 1*H*-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ), which is a well-known soluble guanylate cyclase inhibitor, on relaxation were evaluated in separate series of experiments in which ODQ was added to the organ bath 5 minutes

before the contraction. Responses were recorded by an isometric transducer connected to the MacLab System PowerLab. Addition of the drug vehicle, DMSO, had no appreciable effect on contraction.

Vasodilating potencies expressed as EC_{50}, calculated by linear regression analysis, are reported in Table 2. When the vasodilator experiments were repeated in the presence of 1 μM ODQ a decrease in the vasodilator potencies was observed suggesting that the vasodilating effect of the compounds is NO-cGMP mediated.

Table 2: Vasodilating activity

Compound	**EC_{50} ± SE μM**	**+ ODQ 1 μM EC_{50}± SE μM**
Compound (2)	3.6 ± 0.7	> 100
Compound (4)	21 ± 8	> 100

Example 17

Intraocular pressure (IOP) lowering activity in hypertonic saline-induced IOP increase in rabbits

The present study evaluated the intraocular pressure lowering effect of single application of compound (12) and of ISMN (isosorbide-5-mononitrate) used as reference compound, in an animal model of elevated IOP.

Adults male New Zealand White rabbits weighting 1.8-2.0 Kg were used in the experiments.

Animals were anesthetized using 20 mg/ml/kg of sodium pentobarbital. The increase in IOP was induced by the injection of 0.1 ml of hypertonic saline solution (5%) into the vitreous bilaterally (Krauss et al., 2011, Orihashi et al., 2005).

IOP was measured using a Tono-Pen XL prior to hypertonic saline injection (basal) and at 30, 60, 90 and 120 min thereafter. Vehicle (5% cremophor-EL; 0.3% DMSO; 0.2mg/ml Benzalkonium chloride in PBS pH 6.0,) or compound (12) and ISMN

were instilled as eye drops immediately after hypertonic saline injection. Eyes were randomly assigned to different treatment groups. Vehicle or compounds were directly instilled into the conjunctiva pocket at the desired doses. One drop of 0.2% oxybuprocaine hydrochloride (Novesine, Sandoz) diluted 1:1 with saline was instilled in each eye immediately before each set of pressure measurements.

Results are reported in Table 3 and they are expressed as IOP change (at 30 and 60 minutes following topical administration) versus vehicle and versus IOP at basal before hypertonic saline injection.

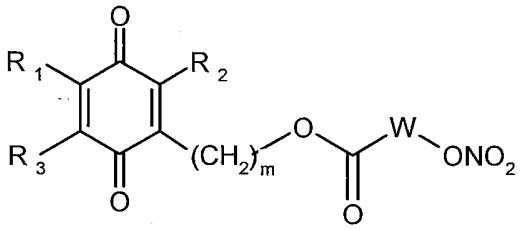
Single application of compound (12) resulted in a significantly higher IOP reduction as compared to ISMN treated group.

Table 3: Intraocular pressure (IOP) lowering activity in hypertonic saline-induced IOP increase in rabbits

Compound	**IOP(mmHg)**	
	30 min	**60 min**
Compound (12)	-9.7 ± 1.3	-8.6 ± 1.3
ISMN	-2.6 ± 3.5	-0.7 ± 2.9

CLAIMS

1. A compound of formula (I)



(I)

or stereoisomers thereof, wherein

R_1 is selected from H, methyl, methoxy;

R_3 is selected from H, methyl, methoxy

or R_1 and R_3 together form –CH=CH-CH=CH-;

R_2 is H, methyl;

m is an integer from 1 to 10;

W is:

1) –(Y)-$(CH_2)_n$-[$CH(ONO_2)$]$_p$-CH_2-

2) –(Y)-$(CH_2)_n$-[X]-$(CH_2)_{n1}$-

3) –$CH(NHR_5)$-$CH(R_4)$-O(CO)-$(CH_2)_n$-[$CH(ONO_2)$]$_p$-CH_2-

wherein

Y is O or a covalent bond;

n is an integer from 1 to 10;

n1 is an integer from 1 to 10

p is 0 or 1;

X is O, NH or S;

R_4 is H or methyl;

R_5 is H, -C(O)CH_3 or -C(O)O-$C(CH_3)_3$.

2. A compound according to claim 1 wherein

R_1 and R_3 are methoxy and

R_2 is methyl.

3. A compound according to claim 2 wherein

W is:

1) $-(Y)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

and Y is O.

4. A compound according to claim 2 wherein

W is:

1) $-(Y)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

and Y is a covalent bond.

5. A compound according to claim 2 wherein

W is:

2) $-CH(NHR_5)-CH(R_4)-O(CO)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$.

6. A compound according to claims 3 to 5 wherein p is 0.

7. A compound according to claim 3 to 5 wherein p is 1.

8. A compound according to claim 2 wherein

W is:

2) $-(Y)-(CH_2)_n-[X]-(CH_2)_{n1}-$

Y is a covalent bond, and

X is O or NH.

9. A compound according to claim 1 wherein

R_1, R_2, and R_3 are methyl.

10. A compound according to claim 9 wherein

W is:

1) $-(Y)-(CH_2)_n-[CH(ONO_2)]_p-CH_2-$

and Y is O.

11. A compound according to claim 9 wherein

W is:

1) –(Y)-$(CH_2)_n$-[$CH(ONO_2)$]$_p$-CH_2-

and Y is a covalent bond.

12. A compound according to claim 9 wherein

W is:

3) –$CH(NHR_5)$-$CH(R_4)$-O(CO)-$(CH_2)_n$-[$CH(ONO_2)$]$_p$-CH_2-.

13. A compound according to claims 10 to 12 wherein p is 0.

14. A compound according to claims 10 to 12 wherein p is 1.

15. A compound according to claim 9 wherein

W is:

2) –(Y)-$(CH_2)_n$-[X]-$(CH_2)_{n1}$-

Y is a covalent bond, and

X is O or NH.

16. A compound according to claim 1 selected from:

2,3-bis(nitrooxy)propyl-10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)decyl carbonate (Compound (1));

10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)decyl 3-(nitrooxy) propyl carbonate (Compound (2));

10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)decyl 6-(nitrooxy) hexyl carbonate (Compound (3));

5,6-bis(nitrooxy)hexyl 10-(4,5-dimethoxy-2-methyl-3,6-dioxo-cyclohexa-1,4-dien-1-yl)decyl carbonate (Compound (4));

[2-(tert-butoxycarbonylamino)-3-[10-(4,5-dimethoxy-2-methyl-3,6-dioxo-cyclohexa-1,4-dien-1-yl)decoxy]-3-oxo-propyl] heptanoate (Compound (5));

10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)decyl 3-(3-(nitrooxy) propylamino)propanoate (Compound (6));

[2-(tert-butoxycarbonylamino)-3-[10-(4,5-dimethoxy-2-methyl -3,6-dioxo-cyclo hexa-1,4-dien-1-yl)decoxy]-3-oxo-propyl] 6-methyloctanoate (compound (7));

3-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dien-1-yl)propyl-4-(nitrooxy)

butanoate (compound (8));

3-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dien-1-yl)propyl 5-(nitrooxy) pentanoate (compound (9));

3-(4,5-Dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)propyl 4-(nitrooxy) butanoate (compound (10));

3-(4,5-Dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)propyl 5-(nitrooxy) pentanoate (compound (11));

3-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)propyl 6-(nitrooxy) hexanoate (compound (12);

[2-amino-3-[10-(4,5-dimethoxy-2-methyl-3,6-dioxo-cyclohexa-1,4-dien-1-yl)deoxy] -3-oxo-propyl] heptanoate (Compound (13));

2-amino-3-(10-(4,5-dimethoxy-2-methyl-3,6-dioxo-cyclohexa-1,4-dienyl) decyloxy)-3-oxopropyl 6,7-bis(nitrooxy) heptanoate (compound (14))

and stereoisomers thereof.

17. A compound of formula (I) according to any of claims 1 to 16 for use as medicament.

18. A compound of formula (I) according to any of claims 1 to 16 for use in treating hypertensive glaucoma, normotensive glaucoma, secondary glaucoma and ocular hypertension.

19. A compound according to any of claims 1 to 16 for use in treating age related macular degeneration, diabetic retinopathy, macular degeneration, inflammatory retinal disease, uveitis.

20. An ophthalmic composition comprising a compound of formula (I) according to any of claims 1 to 16 and at least an ophthalmically acceptable component and/or ophthalmically acceptable vehicle.

21. A composition comprising a compound of formula (I) according to any of claims 1 to 16 and one or more further active ingredients selected from alpha adrenergic agonists, beta blockers, carbonic anhydrase inhibitors, prostaglandin analogs,

non-steroidal anti-inflammatory drugs, or a steroidal anti-inflammatory drugs.

22. A composition according to claim 21 for use in treating hypertensive glaucoma, normotensive glaucoma, secondary glaucoma and ocular hypertension.

23. A composition according to claim 20 for use in treating age related macular degeneration, diabetic retinopathy, macular degeneration, inflammatory retinal disease, uveitis.

24. An ophthalmic composition comprising a composition according to claim 21 and at least an ophthalmically acceptable component and/or ophthalmically acceptable vehicle.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/057611

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C203/04 C07C69/608 A61K31/21 A61P9/08
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)
C07C A61K A61P

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

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/060673 A1 (NICOX SA [FR]) 2 May 2013 (2013-05-02) cited in the application examples 23 and 29 on pages 64 and 77;; claim 1 -----	1-24

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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Date of the actual completion of the international search	Date of mailing of the international search report
29 May 2015	12/06/2015

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/057611

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013060673 A1	02-05-2013	CA 2839390 A1	02-05-2013
		CN 103687843 A	26-03-2014
		CN 103739499 A	23-04-2014
		EP 2707354 A1	19-03-2014
		EP 2722326 A1	23-04-2014
		HK 1197054 A1	02-01-2015
		JP 2014530843 A	20-11-2014
		US 2014342998 A1	20-11-2014
		WO 2013060673 A1	02-05-2013