(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
09 May 2019 (09.05.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/087149 A1

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61P 27/10* (2006.01)
A61K 31/439 (2006.01) *C07D 243/14* (2006.01)
C07D 471/08 (2006.01) *A61K 31/5513* (2006.01)

(21) International Application Number:
PCT/IB2018/058637

(22) International Filing Date:
02 November 2018 (02.11.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/581,073 03 November 2017 (03.11.2017) US
62/749,610 23 October 2018 (23.10.2018) US

(71) Applicant: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, 4056 Basel (CH).

(72) Inventors: **ELLIS, David**; Alcon Laboratories, Inc., 6201 South Freeway, Fort Worth, Texas 76134-2099 (US). **KETELSON, Howard Allen**; Alcon Laboratories, Inc., 6201 South Freeway, Fort Worth, Texas 76134 (US).

(74) Agent: **NOVARTIS AG**; Lichtstrasse 35, 4056 Basel (CH).

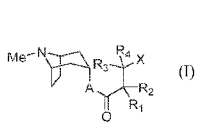
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

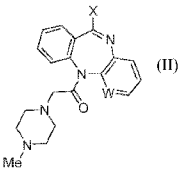
Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: AZABICYCLO AND DIAZEPINE DERIVATIVES FOR TREATING OCULAR DISORDERS



(I)



(II)

FIGURE 1A

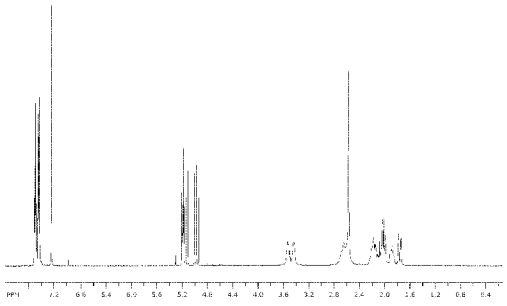
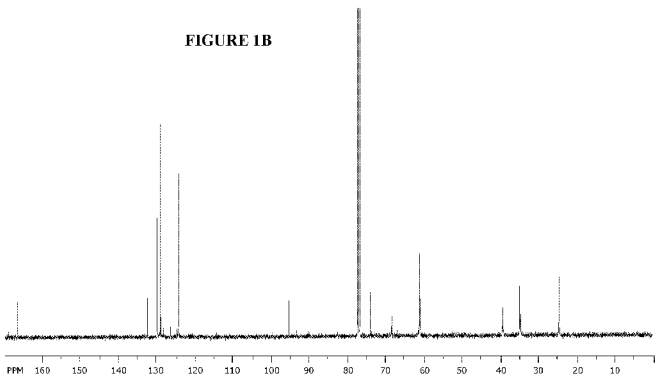


FIGURE 1B



(57) Abstract: The present invention provides in one aspect azabicycio and diazepine derivatives useful as modulators of muscarinic receptors. In another aspect, the present invention provides pharmaceutical compositions for treating ocular diseases, the compositions comprising at least one muscarinic receptor modulator. Formulae (I) & (II):

WO 2019/087149 A1

AZABICYCLO AND DIAZEPINE DERIVATIVES FOR TREATING OCULAR DISORDERS

FIELD OF THE INVENTION

The present invention relates to azabicyclo and diazepine derivatives useful as modulators of muscarinic receptors and methods of treating disease using same.

BACKGROUND OF THE INVENTION

The muscarinic receptor is a target for the excitatory neurotransmitter acetylcholine, and was named based on the selective activation of the receptor by muscarine. The muscarinic receptor is widely distributed throughout human tissues, and is further classified into subtypes of M1 to M5. The modulation of muscarinic receptors has been considered a therapeutic target for disorders ranging from overactive bladder to cognitive disorders (Abrams et al., *Br. J Pharmacol* 2006 July; 148(5): 565-578).

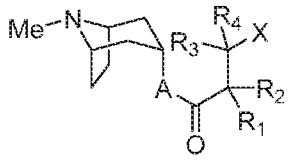
Myopia is an ocular refractive error caused by excessive growth of the eye in a longitudinal direction. This elongation of the eye causes the visual image to be focused in front of the retina and typically results in blurred vision of distant objects. The non-selective muscarinic antagonist atropine has been reported to be effective as a topical 1% drop in the treatment of myopia. (Chua et al., *Ophthalmology* 2006 Dec; 113(12):2285-91). However, numerous side effects were reported, including mydriasis (dilation of the pupil) and blurring of near vision due to cycloplegia (inability to accommodate). Presently, corrective lenses represent the primary means for ameliorating eye-length disorders such as myopia. However, lenses optically correct the refractive errors without treating the underlying cause which is excessive growth of the eye. Thus, there remains a need for methods to treat disorders relating to excessive growth of the eye.

SUMMARY OF THE INVENTION

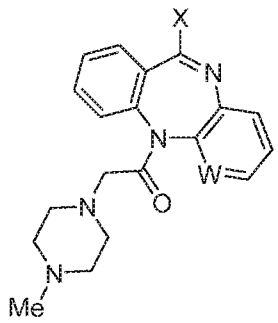
There remains a need for new treatments and therapies for excessive growth of the eye. The invention provides compounds, pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof and combinations thereof, which compounds are muscarinic modulators. The invention further provides methods of treating, preventing, or ameliorating disorders relating

to excessive growth of the eye, comprising administering to a subject in need thereof an effective amount of a muscarinic modulator. Various embodiments of the invention are described herein.

Within certain aspects, provided herein is a compound of formula (I) or formula (II), or a pharmaceutically acceptable salt thereof:



(I)



(II)

wherein

Me = CH_3;

A = O or NR_5;

W = N or CH;

R^1 and R^2 are independently substituted as H, D, hydroxyl, alkoxy, nitrile, halogen atoms, C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl groups optionally substituted with halogen atoms; or

R^1 and R^2 are independently substituted as phenyl or benzyl groups being optionally substituted with one or more substituents selected form C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl groups, halo alkyl groups, hydroxyl, alkoxy, nitrile, nitro, amino, amide, ester, sulfone, sulfoxide, sulfonamide, and halogen atoms; or

R^1 and R^2 are independently substituted with a heterocyclic saturated, unsaturated or aromatic 5- or 6-member ring containing one or more heteroatoms selected from nitrogen, oxygen and sulfur and being optionally substituted with one or more substituents selected

form C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl, halo alkyl groups, hydroxyl, alkoxy, nitrile, nitro, amino, amide, ester, sulfone, sulfoxide or halogen atoms;

R^3 and R^4 are independently substituted with hydrogen, C_1–C_{10} straight or branched or cyclo alkyl or halo alkyl groups or

R^3 and R^4 can combine to form 3- to 6-membered rings;

R^5 = H or C_1–C_{20}, preferably C_1–C_{10}, straight or branched alkyl groups, C_1–C_{10} straight or branched haloalkyl groups;

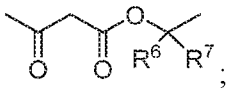
X =–ONO_2, –O–Y–Z, –S–Y–Z, or –NR_5–Y–Z;

Y is a bivalent radical having the following meaning:

a) Straight or branched C_1 – C_{20} alkyl, preferably C_1 – C_{10} alkyl, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxyl, and –ONO_2;

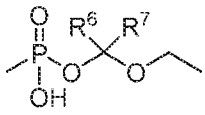
b) –C(O) (C_1 – C_{10} alkyl) – or –C(O)$(CH_2)_n$C(O)O –(C_1 – C_{10} alkyl) – or –(C_1–C_{10} alkyl) –;

c)



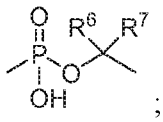
;

d)



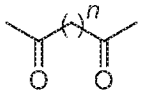
;

e)



;

or f)



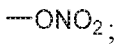
wherein *n* is an integer from 0 to 20;

R^6 and R^7 are independently H or C_1–C_{10} straight or branched alkyl groups, C_1–C_{10} straight or branched haloalkyl groups; or

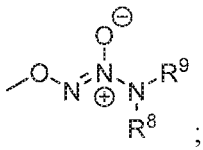
R^6 and R^7 can combine to form 3- to 6-membered rings; and

Z is a monovalent radical having the following meaning:

a)

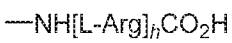


b)



; or

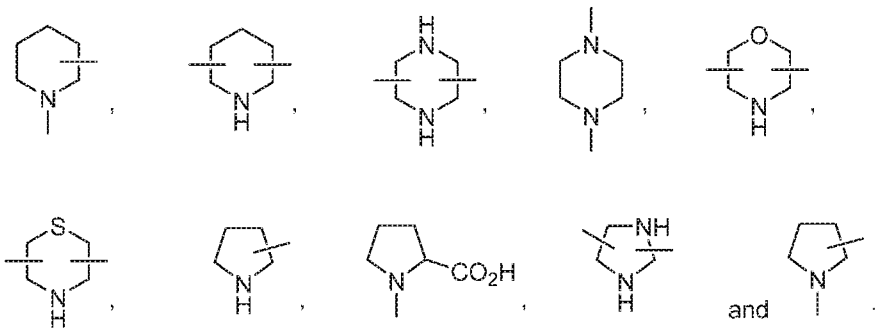
c)



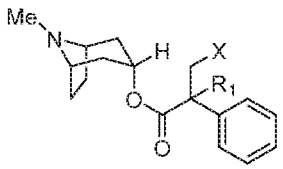
wherein *h* is an integer from 0 to 10;

R^8 and R^9 are independently substituted as $C_1 - C_{20}$ alkyl, preferably $C_1 - C_{10}$ alkyl, being optionally substituted with one or more substituents selected from hydroxyl, amino, ester, carboxylic acid, and halogen atoms; or

R^8 and R^9 can combine to form 3- to 6-membered rings containing one or more heteroatoms, which are selected from the group consisting of:



In some embodiments, the compound of formula (I) has the following formula (IA):



(IA)

wherein R^1 = H, D, OH, halogen, C_1–C_{10} straight or branched alkyl, phenyl or benzyl, a heterocyclic saturated, unsaturated or aromatic 5- or 6-member ring, containing one or more heteroatoms selected from nitrogen, oxygen and sulfur;

W = N or CH;

X = $–ONO_2$, –O–Y–Z, –S–Y–Z, or $–NR_5$–Y–Z;

and Y and Z are as defined above.

In another aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount (preferably from about 0.01 to about 10.0 weight percent of, more preferably from about 0.01 to about 5 weight/volume percent of or from about 0.1 to 5.0 weight percent of) (a) a compound of the present invention and/or (b) a pharmaceutically acceptable salt thereof; and (2) one or more pharmaceutically acceptable carriers.

In yet another aspect, the invention provides a pharmaceutical composition comprising: (1) a compound of the present invention and/or a pharmaceutically acceptable salt thereof; and (2) one or more pharmaceutically acceptable carriers.

In another aspect, the invention provides a combination, in particular a pharmaceutical combination, comprising: (1) a therapeutically effective amount of (preferably from about 0.01 to about 10.0 weight percent, more preferably from about 0.01 to about 5 weight/volume percent of or from about 0.1 to 5.0 weight percent of) (a) a compound of the present invention and/or (b) a pharmaceutically acceptable salt thereof; and (2) one or more therapeutically active agents. In yet another aspect, the invention provides a combination, in particular a pharmaceutical combination, comprising: (1) a compound of the present invention and/or a pharmaceutically acceptable salt thereof; and (2) one or more therapeutically active agents.

Specific preferred embodiments of the invention will become evident from the following more detailed description of certain preferred embodiments and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1A is a ^{1}H NMR spectrum of (*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-fluoro-3-(nitrooxy)-2-phenylpropanoate. FIGURE 1B is a ^{13}C NMR spectrum of (*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-fluoro-3-(nitrooxy)-2-phenylpropanoate.

FIGURE 2A is a ^{1}H NMR spectrum of 2-Fluoro-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl 6-(nitrooxy)hexanoate. FIGURE 2B is a ^{13}C NMR spectrum of 2-Fluoro-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl 6-(nitrooxy)hexanoate.

FIGURE 3A is a ^{1}H NMR spectrum of (*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-methyl-3-(nitrooxy)-2-phenylpropanoate. FIGURE 3B is a ^{13}C NMR spectrum of (*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-methyl-3-(nitrooxy)-2-phenylpropanoate.

FIGURE 4A is a ^{1}H NMR spectrum of 2-Methyl-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl-6-(nitrooxy)hexanoate. FIGURE 4B is a ^{13}C NMR spectrum of 2-Methyl-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl-6-(nitrooxy)hexanoate.

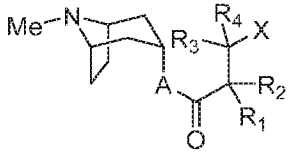
FIGURE 5A is a ^{1}H NMR spectrum of (*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-benzyl-3-(nitrooxy)-2-phenylpropanoate. FIGURE 5B is a ^{13}C NMR spectrum of (*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-benzyl-3-(nitrooxy)-2-phenylpropanoate.

FIGURE 6A is a ^{1}H NMR spectrum of 2-Benzyl-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl-6-(nitrooxy)hexanoate. FIGURE 6B is a ^{13}C NMR spectrum of 2-Benzyl-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl-6-(nitrooxy)hexanoate.

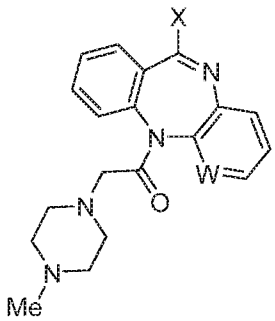
FIGURE 7A is a ^{1}H NMR spectrum of 6-((11-(2-(4-Methylpiperazin-1-yl)acetyl)-11*H*-benzo[e]pyrido[3,2-b][1,4]diazepin-6-yl)oxy)hexyl nitrate. FIGURE 7B is a ^{13}C NMR spectrum of 6-((11-(2-(4-Methylpiperazin-1-yl)acetyl)-11*H*-benzo[e]pyrido[3,2-b][1,4]diazepin-6-yl)oxy)hexyl nitrate.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to classes of compounds each having an atropine or pirenzepine residue and pharmaceutically acceptable salts thereof. In specific embodiments, the invention provides a compound of formula (I) or (II):



(I)



(II)

wherein

Me = CH_3;

A = O or NR_5;

W = N or CH;

R^1 and R^2 are independently substituted as H, D, hydroxyl, alkoxy, nitrile, halogen atoms, C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl groups optionally substituted with halogen atoms; or

R^1 and R^2 are independently substituted as phenyl or benzyl groups being optionally substituted with one or more substituents selected form C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl groups, halo alkyl groups, hydroxyl, alkoxy, nitrile, nitro, amino, amide, ester, sulfone, sulfoxide, sulfonamide, and halogen atoms; or

R^1 and R^2 are independently substituted with a heterocyclic saturated, unsaturated or aromatic 5- or 6-member ring containing one or more heteroatoms selected from nitrogen, oxygen and sulfur and being optionally substituted with one or more substituents selected form C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl, halo alkyl groups, hydroxyl, alkoxy, nitrile, nitro, amino, amide, ester, sulfone, sulfoxide or halogen atoms;

R^3 and R^4 are independently substituted with hydrogen, C_1–C_{10} straight or branched or cyclo alkyl or halo alkyl groups or

R^3 and R^4 can combine to form 3- to 6-membered rings;

R^5 = H or C_1–C_{20}, preferably C_1–C_{10}, straight or branched alkyl groups, C_1–C_{10} straight or branched haloalkyl groups;

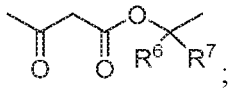
X =–ONO_2, –O–Y–Z, –S–Y–Z, or –NR_5–Y–Z;

Y is a bivalent radical having the following meaning:

a) Straight or branched $C_1 – C_{20}$ alkyl, preferably $C_1 – C_{10}$, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxyl, and –ONO_2;

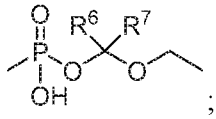
b) –C(O) ($C_1 – C_{10}$ alkyl) – or –C(O)$(CH_2)_n$C(O)O –($C_1 – C_{10}$ alkyl) – or –(C_1–C_{10} alkyl) –;

c)



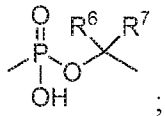
;

d)



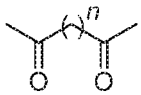
;

e)



; or

f)



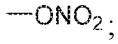
wherein *n* is an integer from 0 to 20;

R^6 and R^7 are independently H or C_1–C_{10}, straight or branched alkyl groups, C_1–C_{10} straight or branched haloalkyl groups ; or

R^6 and R^7 can combine to form 3- to 6-membered rings; and

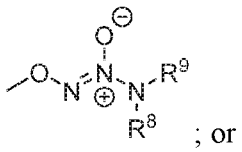
Z is a monovalent radical having the following meaning:

a)



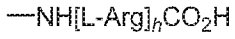
;

b)



; or

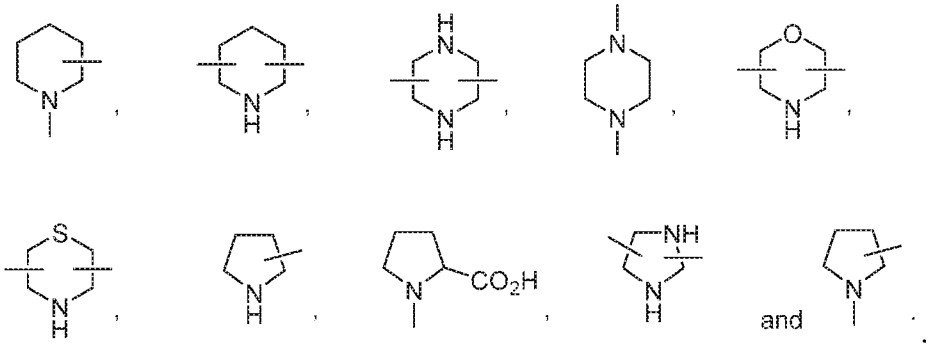
c)



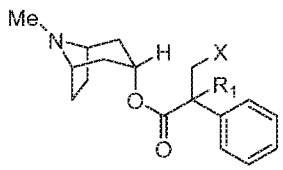
wherein *h* is an integer from 0 to 10;

R^8 and R^9 are independently substituted as $C_1 - C_{20}$ alkyl, preferably $C_1 - C_{10}$, being optionally substituted with one or more substituents selected from hydroxyl, amino, ester, carboxylic acid, and halogen atoms; or

R^8 and R^9 can combine to form 3- to 6-membered rings containing one or more heteroatoms which are selected from the group consisting of:



In some embodiments, the compound of formula (I) has formula (IA):



(IA)

wherein R^1 = H, D, OH, halogen, $C_1 - C_{10}$ straight or branched alkyl, phenyl or benzyl, a heterocyclic saturated, unsaturated or aromatic 5- or 6-member ring, containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur;

W = N or CH;

X = =–ONO_2, –O–Y–Z, –S–Y–Z, or –NR_5–Y–Z;

and Y and Z are as described above.

In some embodiments, the invention relates to a method of treating a mammalian subject having or at risk of having an ocular disorder, comprising administering to the subject an effective amount of a compound according to formula (I) or formula (II).

DEFINITIONS

Unless specified otherwise, the term “compounds of the present invention” or “compound of the present invention” refers to compounds of formula (I) or formula (II), subformulae thereof, and exemplified compounds, and salts thereof, as well as all stereoisomers (including diastereoisomers and enantiomers), rotamers, tautomers and isotopically labeled compounds (including deuterium substitutions), as well as inherently formed moieties.

The language "effective amount" of the compounds of the invention, described infra, refers to that amount of a therapeutic compound necessary or sufficient to perform its intended function within a mammal, e.g., treat a muscarinic receptor associated disorder, or a disease state in a mammal. An effective amount of the therapeutic compound can vary according to factors such as the amount of the causative agent already present in the mammal, the age, sex, and weight of the mammal, and the ability of the therapeutic compounds of the present invention to affect the muscarinic receptor associated disorder in the mammal. One of ordinary skill in the art would be able to study the aforementioned factors and make a determination regarding the effective amount of the therapeutic compound without undue experimentation. An in vitro or in vivo assay also can be used to determine an "effective amount" of the therapeutic compounds described infra. The ordinarily skilled artisan would select an appropriate amount of the therapeutic compound for use in the aforementioned assay or as a therapeutic treatment.

The phrase "ophthalmically compatible" is art-recognized and refers to formulations, polymers and other materials and/or dosage forms which are suitable for use in contact with the ocular tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio as determined by one of ordinary skill in the art.

As used herein, a pharmaceutical composition is a composition suitable for pharmaceutical use. A composition suitable for pharmaceutical use may be sterile, homogeneous and/or isotonic. Pharmaceutical compositions may be prepared in certain embodiments in an aqueous form, for example in a pre-filled syringe or other single- or multi-dose container. In certain embodiments, the pharmaceutical compositions of the invention are ophthalmically compatible and suitable for ophthalmic administration to a human subject by, for example, topical or other known methods of delivery. In another embodiment, the pharmaceutical compositions of the invention are suitable for intravitreal administration. In yet another embodiment, the pharmaceutical compositions of the invention are suitable for administration by intravitreal infusion. In yet another embodiment, the pharmaceutical compositions are administered orally.

As used herein, the term "alkyl" is intended to include branched, straight chain and cyclic, substituted or unsubstituted saturated aliphatic hydrocarbon groups. Alkyl groups can comprise about 1 to about 24 carbon atoms ("C_1-C_{24}"), about 7 to about 24 carbon atoms ("C_7-C_{24}"), about 8 to about 24 carbon atoms ("C_8-C_{24}"), or about 9 to about 24 carbon atoms ("C_9-C_{24}"). Alkyl groups can also comprise about 1 to about 8 carbon atoms ("C_1-C_8"), about 1 to about 6 carbon atoms ("C_1-C_6"), or about 1 to about 3 carbon atoms ("C_1-C_3"). Examples of C_1-C_6 alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl and n-hexyl radicals.

As used herein, the term "C_{2-6}alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, having from two to six carbon atoms, which is attached to the rest of the molecule by a single bond. The terms "C_2-C_{20} alkenyl" and "C_2-C_{10} alkenyl" are to be construed accordingly. Examples of C_{2-6}alkenyl include, but are not limited to, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, pent-4-enyl and penta-1,4-dienyl.

As used herein, the term "C_{2-6}alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to six carbon atoms, and which is attached to the rest of the molecule by a single bond. The term "C_{2-4}alkynyl" is to be construed accordingly. Examples of C_{2-6}alkynyl include, but are not limited to, ethynyl, prop-1-ynyl, but-1-ynyl, pent-1-ynyl, pent-4-ynyl and penta-1,4-diynyl.

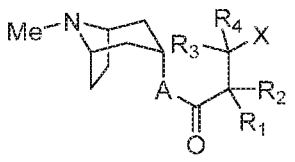
As used herein, the term "C_{1-6}alkoxy" refers to a radical of the formula -OR_a where R_a is a C_{1-6}alkyl radical as generally defined above. Examples of C_{1-6}alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, and hexoxy.

"Halogen" refers to bromo, chloro, fluoro or iodo.

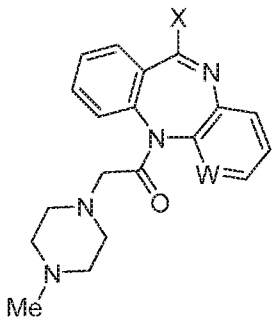
As used herein, the term "heterocyclyl" or "heterocyclic" refers to a stable 5- or 6-membered non-aromatic monocyclic ring radical which comprises 1, 2, or 3, heteroatoms individually selected from nitrogen, oxygen and sulfur. The heterocyclyl radical may be bonded via a carbon atom or heteroatom. Examples of heterocyclyl include, but are not limited to, azetidinyl, oxetanyl, pyrrolinyl, pyrrolidyl, tetrahydrofuryl, tetrahydrothienyl, piperidyl, piperazinyl, tetrahydropyranyl, morpholinyl or perhydroazepinyl.

As used herein, the term "heteroaryl" refers to a 5- or 6-membered aromatic monocyclic ring radical which comprises 1, 2, 3 or 4 heteroatoms individually selected from nitrogen, oxygen and sulfur. The heteroaryl radical may be bonded via a carbon atom or heteroatom. Examples of heteroaryl include, but are not limited to, furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, pyrimidyl or pyridyl.

The present invention provides in certain embodiments novel pharmaceutical formulations, in particular novel pharmaceutical formulations in which the active ingredient comprises a muscarinic modulator of the formula (I) or formula (II) or pharmaceutically acceptable salts or stereoisomers thereof:



(I)



(II)

wherein

Me = CH_3;

A = O or NR_5;

W = N or CH;

R^1 and R^2 are independently substituted as H, D, hydroxyl, alkoxy, nitrile, halogen atoms, C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl groups optionally substituted with halogen atoms; or

R^1 and R^2 are independently substituted as phenyl or benzyl groups being optionally substituted with one or more substituents selected form C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl groups, halo alkyl groups, hydroxyl, alkoxy, nitrile, nitro, amino, amide, ester, sulfone, sulfoxide, sulfonamide, and halogen atoms; or

R^1 and R^2 are independently substituted with a heterocyclic saturated, unsaturated or aromatic 5- or 6-member ring containing one or more heteroatoms selected from nitrogen, oxygen and sulfur and being optionally substituted with one or more substituents selected form C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl, halo alkyl groups, hydroxyl, alkoxy, nitrile, nitro, amino, amide, ester, sulfone, sulfoxide or halogen atoms;

R^3 and R^4 are independently substituted with hydrogen, C_1–C_{10} straight or branched or cyclo alkyl or halo alkyl groups or

R^3 and R^4 can combine to form 3- to 6-membered rings;

R^5 = H or C_1–C_{20}, preferably C_1–C_{10}, straight or branched alkyl groups, C_1–C_{10} straight or branched haloalkyl groups;

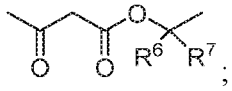
X =–ONO_2, –O–Y–Z, –S–Y–Z, or –NR_5–Y–Z;

Y is a bivalent radical having the following meaning:

a) Straight or branched alkyl, preferably, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxyl, and $–ONO_2$;

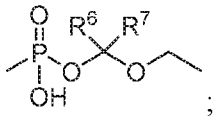
b) $–C(O)\ (C_1 – C_{10}\ alkyl) –$ or $–C(O)(CH_2)_nC(O)O\ –(C_1 – C_{10}\ alkyl) –$ or $–(C_1–C_{10}\ alkyl) –$;

c)



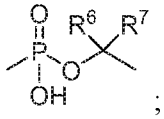
;

d)



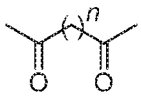
;

e)



;

or f)



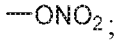
wherein *n* is an integer from 0 to 20;

R^6 and R^7 are independently H or $C_1–C_{10}$, straight or branched alkyl groups, $C_1–C_{10}$ straight or branched haloalkyl groups ; or

R^6 and R^7 can combine to form 3- to 6-membered rings; and

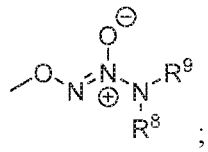
Z is a monovalent radical having the following meaning:

a)

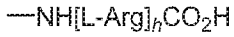


;

b)



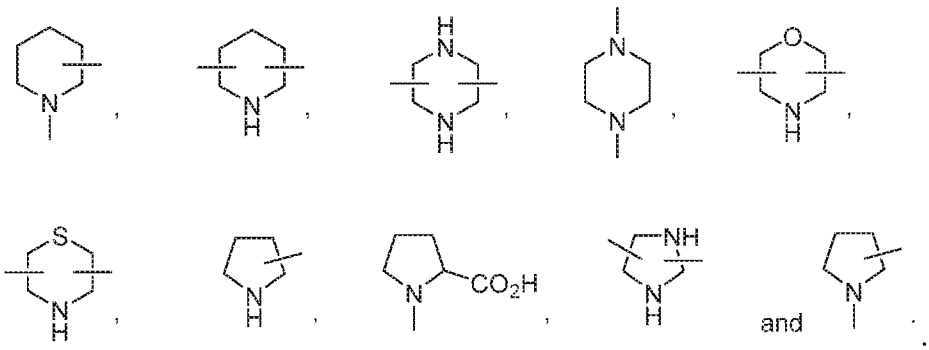
or c)



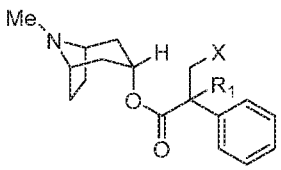
wherein *h* is an integer from 0 to 10;

R^8 and R^9 are independently substituted as $C_1 - C_{20}$ alkyl, preferably $C_1 - C_{10}$, being optionally substituted with one or more substituents selected from hydroxyl, amino, ester, carboxylic acid, and halogen atoms; or

R^8 and R^9 can combine to form 3- to 6-membered rings containing one or more heteroatoms, which are selected from the group consisting of:



In some embodiments, the compound of formula (I) has the following formula (IA):



(IA)

wherein R^1 = H, D, OH, halogen, $C_1 - C_{10}$ straight or branched alkyl, phenyl of benzyl, a heterocyclic saturated, unsaturated or aromatic 5- or 6-member ring, containing one or more heteroatoms selected from nitrogen, oxygen and sulfur;

W = N or CH;

X = –ONO_2, –O–Y–Z, –S–Y–Z, or –NR_5–Y–Z;

and Y and Z have the same meanings as described above.

In some embodiments, compounds of formula (I) and formula (II) are selected from the group consisting of:

(*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-fluoro-3-(nitrooxy)-2-phenylpropanoate,

2-Fluoro-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl 6-(nitrooxy)hexanoate,

(*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-methyl-3-(nitrooxy)-2-phenylpropanoate,

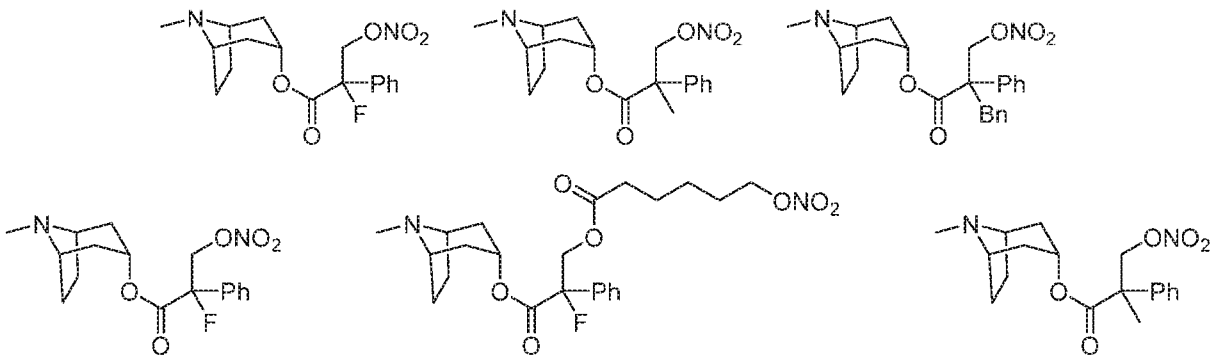
2-Methyl-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl-6-(nitrooxy)hexanoate,

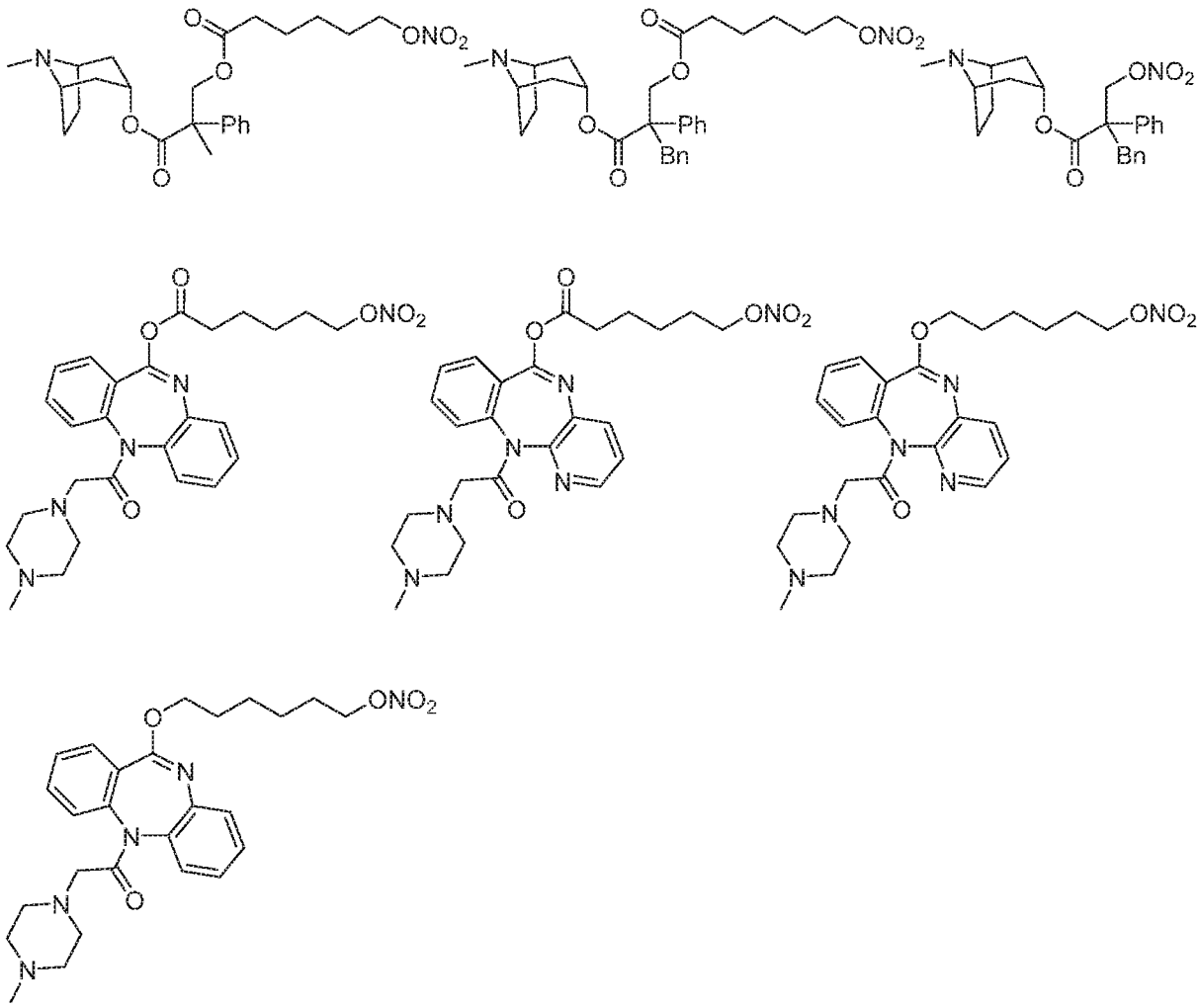
(*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-benzyl-3-(nitrooxy)-2-phenylpropanoate,

2-Benzyl-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl-6-(nitrooxy)hexanoate, and

6-((11-(2-(4-Methylpiperazin-1-yl)acetyl)-11*H*-benzo[e]pyrido[3,2-b][1,4]diazepin-6-yl)oxy)hexyl nitrate.

Additional compounds of the present invention include the following:





In some embodiments, the invention relates to a method of treating a mammalian subject having or at risk of having an ocular disorder, said method comprising administering to the subject an effective amount of a compound according to formula (I) or formula (II). In particular embodiments, the ocular disorder is myopia.

The following paragraphs provide examples of compounds according to the present invention:

EXAMPLES

NMR spectra were taken on a Bruker 400 MHz spectrometer or a Bruker 300 MHz spectrometer. LCMS methods are detailed below (unless otherwise stated):

Standard LCMS method:

Instrumentation	Acquity H-Class (quaternary pump/PDA detector) + QDa Mass Spectrometer

Column	Acquity UPLC CSH C18 1.7 µm, 50 × 2.1 mm at 40°C		
Mobile Phase A	0.1% Aqueous formic acid (v/v)		
Mobile Phase B	0.1% Formic acid in acetonitrile (v/v)		
Flow	1.0 mL/min		
Gradient Program	Time (mins)	% A	%B
	0.0	97	03
	1.5	01	99
	1.9	01	99
	2.0	97	03
	2.5	97	03
Sample	1 µL injection (Open Access)		
Detectors	UV, diode array 190-400 nm		
	MS, mass 160–800 (or 60–800 for LM or 300–1200 for HM method) in ES+ & ES-		

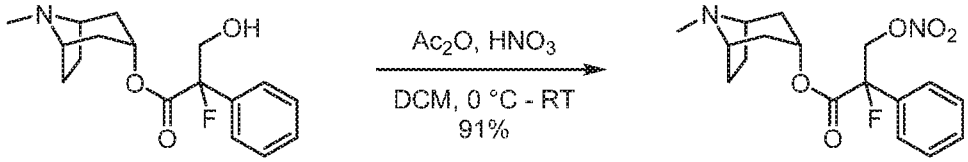
QC LCMS method:

Instrumentation	Acquity UPLC (binary pump/PDA detector) + ZQ Mass Spectrometer		
Column	ACQUITY UPLC BEH C_{18} 1.7 µm, 100 × 2.1 mm, maintained at 40°C		
Mobile Phase A	0.1% Aqueous formic acid (v/v)		
Mobile Phase B	0.1% Formic acid in acetonitrile (v/v)		
Flow	0.4 mL/min		
Gradient Program	Time (mins)	% A	%B
	0.0	95	05
	0.4	95	05
	6.0	05	95
	6.8	05	95
	7.0	95	05
	8.0	95	05
Sample	1 µL injection of a 0.2-0.5mg/ml solution in an appropriate solvent at 20°C		
Detectors	UV, diode array 200-500 nm		
	MS, mass 100-800 (or –1500 for HM method) in ES+ & ES- (no split to MS)		
Data Analysis	Peak area percentage (APCT) with an integration threshold of 0.2% (relative)		

Abbreviations:

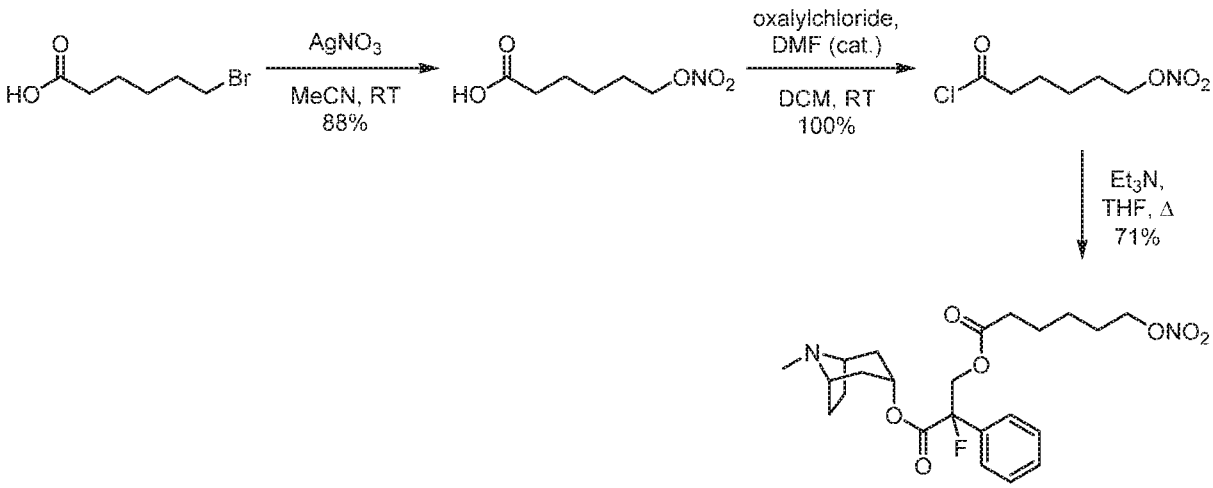
DAST	Diethylaminosulfur trifluoride
DCM	Dichloromethane
DMF	Dimethylformamide
RT	Room Temperature

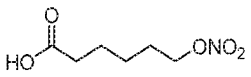
Synthetic Scheme of Example 1: (*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-fluoro-3-(nitrooxy)-2-phenylpropanoate



To a solution of acetic anhydride (2.0 mL, 20.8 mmol) in DCM (80 mL) at 0°C was added, dropwise fuming nitric acid (0.71 mL, 16.9 mmol) and the reaction mixture stirred at 0°C for 5 minutes. (*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl 2-fluoro-3-hydroxy-2-phenylpropanoate (4.0 g, 13.0 mmol) was added as a solution in DCM (15 mL) and the reaction stirred at 0°C for 5 h. then at RT for 16 h. LCMS indicated ~ 30 % product. Fuming nitric acid (0.71 mL, 16.9 mmol) was added to a solution of acetic anhydride (2.0 mL, 20.8 mmol) in DCM (10 mL) at 0°C and the mixture stirred at 0°C for 5 min. The resulting solution was added to the reaction and stirred at RT for 1 h. The reaction mixture was diluted with 1N NaOH solution and extracted with DCM. The combined organic fractions were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by chromatography, eluting with (0-5% 7N NH_3 in MeOH)/DCM, to yield the title compound as a straw coloured oil (4.2 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.41 (5H, m), 5.22-5.08 (2H, m), 4.97 (1H, dd, J=13.8, 12.3 Hz), 3.58-3.37 (2H, m), 2.75-2.52 (5H, m), 2.25-1.96 (4H, m), 1.92-1.81 (1H, m), 1.76 (1H, d, J = 15.4 Hz). ^{13}C NMR (100 MHz, CDCl3): δ 166.5, 132.7, 130.1, 129.2, 124.3, 94.4 (d, J = 201.3 Hz), 73.8, 68.3, 61.0, 39.2, 34.7, 24.4; LCMS (ESI) $[M+H]^+$ 353, R_t = 1.30 min. The ^{1}H NMR and ^{13}C NMR spectra for the title compound are shown in FIGURE 1A and 1B respectively.

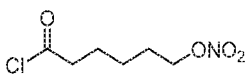
Synthetic Scheme of Example 2: 2-Fluoro-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl 6-(nitrooxy)hexanoate





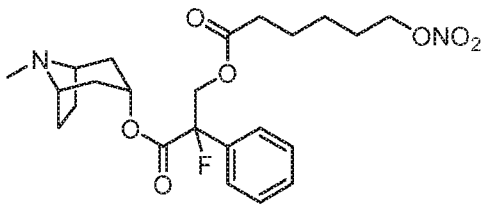
6-(Nitrooxy)hexanoic acid

To a solution of 6-bromohexanoic acid (50.0 g, 0.26 mol) in MeCN (250 mL) was added silver nitrate (65.3 g, 0.38 mol) and the suspension stirred at 50°C for 3 h. The reaction mixture was cooled to RT and filtered and the filtrate was concentrated *in vacuo* causing more solids to precipitate. The residue was diluted with DCM, filtered and the filtrate washed with water. The organic fraction was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the product as a straw coloured oil (40.1 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.15 (1H, br s), 4.46 (2H, t, J = 6.6 Hz), 2.39 (2H, t, J = 7.4 Hz), 1.76 (2H, pent, J = 6.6 Hz), 1.69 (2H, pent, J = 7.0 Hz), 1.52-1.42 (2H, m).



6-Chloro-6-oxohexyl nitrate

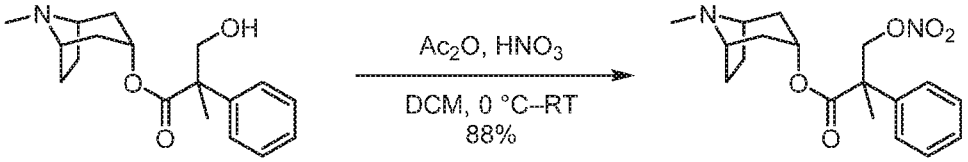
To a solution of 6-(nitrooxy)hexanoic acid (2.5 g, 14.1 mmol) in DCM at RT was added 1 drop of DMF followed by oxalyl chloride (1.8 mL, 21.1 mmol), causing effervescence. The reaction mixture was stirred at RT for 1.5 h. and was then concentrated *in vacuo* to produce the product as a semi-solid (2.76 g, quant.). The material was used crude in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (2H, t, J = 6.5 Hz), 2.92 (2H, t, J = 7.2 Hz), 1.81-1.71 (4H, m), 1.54-1.44 (2H, m).



2-Fluoro-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl 6-(nitrooxy)hexanoate

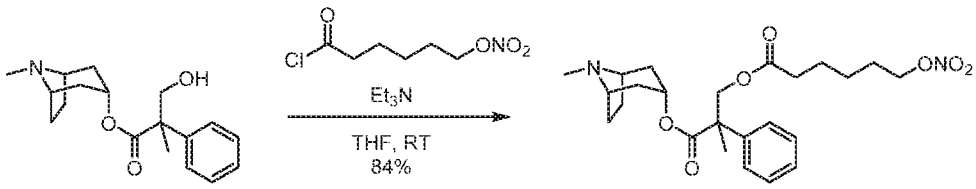
To a solution of (*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl-2-fluoro-3-hydroxy-2-phenyl propanoate (3.5 g, 11.4 mmol) in THF (50 mL) was added 6-chloro-6-oxohexyl nitrate (2.78 g, 14.2 mmol) and triethylamine (2.5 mL, 18.2 mmol). The reaction mixture was stirred at reflux for 30 min. then diluted with water and extracted with ethyl acetate. The combined organic fractions were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by chromatography, eluting with (0-10% 7N NH_3 in MeOH)/DCM. The material contained small impurities and was re-purified similarly to give the title compound as an orange oil (4.2 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.49 (2H, m), 7.46-7.36 (3H, m), 5.08 (1H, t, J = 5.32 Hz), 4.83-4.63 (2H, m), 4.43 (2H, t, J = 6.4 Hz), 3.13-2.99 (2H, m), 2.35 (2H, t, J = 7.2 Hz), 2.25 (3H, s), 2.18-2.07 (2H, m), 2.00-1.84 (2H, m), 1.83-1.56 (8, m), 1.45-1.36 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 167.4, 134.2, 129.3, 128.7, 124.7, 94.9 (d, J = 199.1 Hz), 72.9, 70.2, 66.5, 59.5, 40.4, 36.4, 33.6, 26.4, 25.4, 25.1, 24.2; LCMS (ESI) $[M+H]^+$ 467, R_t = 1.75 min. The ^{1}H NMR and ^{13}C NMR spectra for the title compound are shown in FIGURE 2A and 2B respectively.

Synthetic Scheme of Example 3: (*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-methyl-3-(nitrooxy)-2-phenylpropanoate



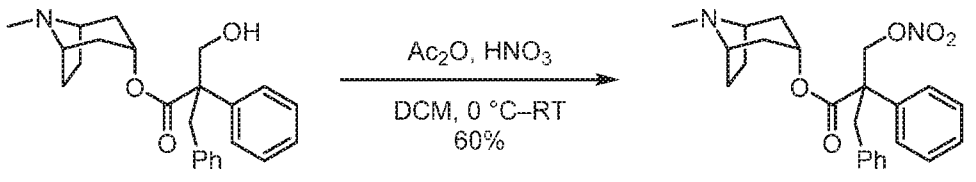
A solution of acetic anhydride (3.30 g, 32.30 mmol) in DCM (20 mL) was cooled in an ice-water bath and nitric acid (fuming, 1.66 g, 26.37 mmol) added. After 10 minutes this was added dropwise during 20 minutes to a solution of (*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl 2-methyl-3-hydroxy-2-phenylpropanoate (2.00 g, 6.59 mmol) in DCM (60 mL). The reaction mixture was stirred at RT for 18 H before adding to H_2O – DCM and basified to pH>10 using NaOH. DCM extracts were washed with H_2O and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow gum. Crude product was dissolved in Et_2O and extracted into dil HCl. This aqueous solution was added to fresh Et_2O, basified to pH>10 using NaOH and Et_2O extracts washed with H_2O and brine, then dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the title compound as a colourless oil (2.03 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.28 (5H, m), 5.09-4.99 (2H, m), 4.67 (1H, d, J = 10.3 Hz), 3.05-2.91 (2H, m), 2.20 (3H, s), 2.15-2.01 (2H, m), 1.91-1.80 (1H, m), 1.79-1.68 (1H, m), 1.73 (3H, s), 1.65-1.44 (3H, m), 1.27-1.19 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 138.4, 129.0, 128.1, 125.8, 68.9, 59.5, 49.5, 40.4, 36.5, 36.3, 25.4, 25.0, 19.8; LCMS (ESI) $[M+H]^+$ 349, R_t = 0.87 min.; QC LCMS (ESI) $[M+H]^+$ 349.1, R_t = 3.14 min. The ^{1}H NMR and ^{13}C NMR spectra for the title compound are shown in FIGURE 3A and 3B respectively.

Synthetic Scheme of Example 4: 2-Methyl-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl-6-(nitrooxy)hexanoate



A solution of (*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl-2-methyl-3-hydroxy-2-phenyl propanoate (3.00 g, 9.89 mmol) and triethylamine (4.1 mL, 29.66 mmol) in THF (40 mL) was treated with dropwise addition of 6-chloro-6-oxohexyl nitrate (4.84 g, 24.72 mmol) during 20 minutes at RT. The reaction mixture was stirred at RT for 4 hours before adding to H_2O – EtOAc and basified to pH>10 using 1N NaOH. EtOAc extracts were washed with H_2O and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow gum. Crude product was dissolved in DCM, loaded onto a silica cartridge (80 g) and eluted using a gradient of 7N NH_3 in MeOH – EtOAc (0-10%). Relevant fractions were concentrated *in vacuo* to give the title compound as a pale yellow oil (3.86 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (5H, m), 5.03 (1H, t, J = 5.4 Hz), 4.63 (1H, d, J = 10.8 Hz), 4.48-4.39 (3H, m), 3.03-2.93 (2H, m), 2.31 (2H, d, J = 7.3 Hz), 2.21 (3H, s), 2.14-2.02 (2H, m), 1.86-1.44 (12H, m), 1.43-1.31 (3H, m): ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 140.0, 128.7, 127.5, 125.9, 72.9, 69.0, 68.2, 59.5, 50.1, 40.3, 36.4, 36.3, 33.9, 26.5, 25.3, 25.1, 25.0, 24.3, 20.7; LCMS (ESI) $[M+H]^+$ 463, R_t = 1.11 min. QC LCMS (ESI) $[M+H]^+$ 463.1, R_t = 3.63 min. The ^{1}H NMR and ^{13}C NMR spectra for the title compound are shown in FIGURE 4A and 4B respectively.

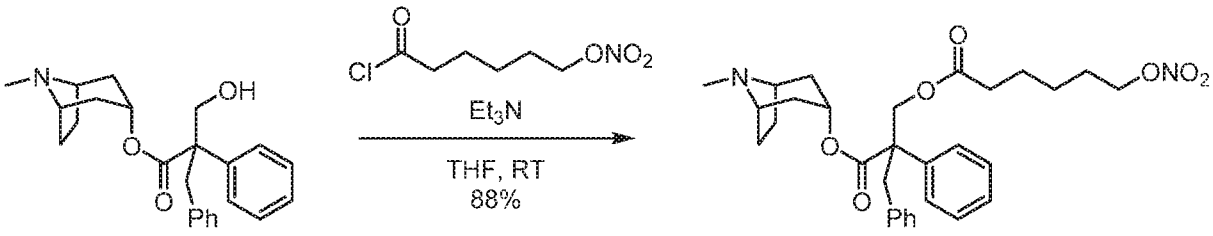
Synthetic Scheme of Example 5: (*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-benzyl-3-(nitrooxy)-2-phenylpropanoate



A solution of acetic anhydride (2.64 g, 25.82 mmol) in DCM (20 mL) was cooled in an ice-water bath and nitric acid (fuming, 1.33 g, 21.08 mmol) added. After 10 minutes this was added

dropwise during 20 minutes to a solution of (*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl 2-benzyl-3-hydroxy-2-phenylpropanoate (2.00 g, 5.27 mmol) in DCM (60 mL). The reaction mixture was stirred at RT for 18 H before adding to H_2O – DCM and basified to pH>10 using NaOH. DCM extracts were washed with H_2O and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow gum. Crude product was triturated using 25% EtOAc – isohexane and a dark yellow solid removed by filtration. The filtrate was concentrated *in vacuo* to give a yellow solid. This solid was triturated using 10% EtOAc – isohexane, solids filtered off and dried *in vacuo* to give the title compound as a pale yellow solid (1.34 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.29 (3H, m), 7.24-7.16 (5H, m), 6.92-6.84 (2H, m), 5.10 (1H, t, J = 5.3 Hz), 4.87-4.76 (2H, m), 3.58-3.38 (2H, m), 3.02-2.91 (2H, m), 2.19 (3H, s), 2.17-2.02 (2H, m), 1.80-1.67 (2H, m), 1.65-1.44 (2H, m), 1.39-1.29 (1H, m), 1.18-1.09 (1H, m): ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 138.1, 135.5, 130.1, 129.0, 128.5, 128.0, 127.2, 126.1, 72.7, 69.1, 59.5, 53.6, 40.4, 39.3, 36.4, 25.1, 25.0; LCMS (ESI) $[M+H]^+$ 425, R_t = 1.06 min.; QC LCMS (ESI) $[M+H]^+$ 425.2, R_t = 3.72 min. The ^{1}H NMR and ^{13}C NMR spectra for the title compound are shown in FIGURE 5A and 5B respectively.

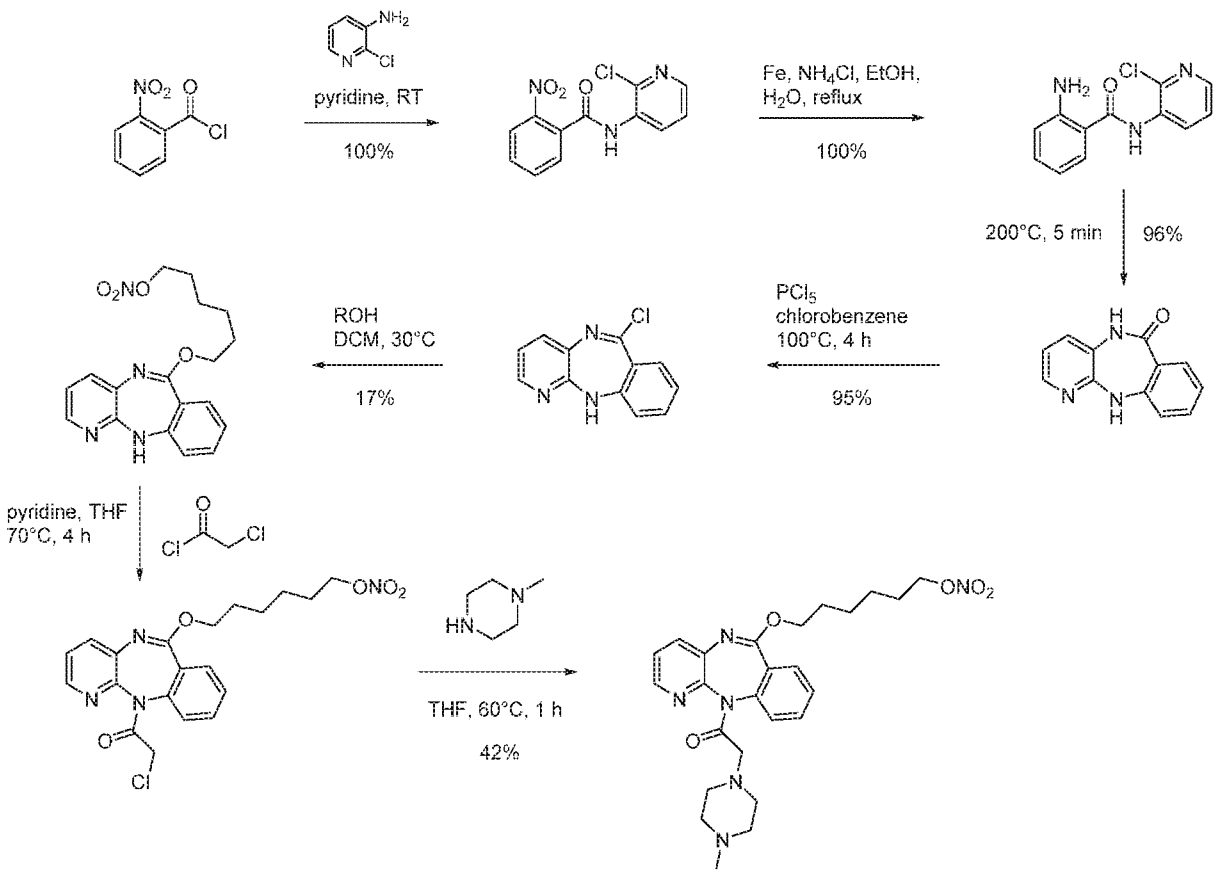
Synthetic Scheme of Example 6: 2-Benzyl-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl-6-(nitrooxy)hexanoate

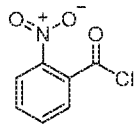


A suspension of (*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl 2-benzyl-3-hydroxy-2-phenylpropanoate (3.75 g, 9.89 mmol) and triethylamine (4.1 mL, 29.66 mmol) in THF (40 mL) was treated with dropwise addition of 6-chloro-6-oxohexyl nitrate (4.84 g, 24.72 mmol) during 30 minutes at RT. The reaction mixture was stirred at RT for 20 hours before adding to H_2O – EtOAc and basified to pH>10 using 1N NaOH. EtOAc extracts were washed with H_2O and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow gum. Crude product was dissolved

in DCM, loaded onto a silica cartridge (80 g) and eluted using a gradient of 7N NH_3 in MeOH – EtOAc (0-10%). Relevant fractions were concentrated *in vacuo* to give the title compound as a pale yellow oil (4.69 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (3H, m), 7.20-7.11 (5H, m), 6.82-6.76 (2H, m), 5.07 (1H, t, J = 5.3 Hz), 4.58 (1H, d, J = 11.0 Hz), 4.47 (1H, d, J = 10.6 Hz), 4.44 (2H, t, J = 6.5 Hz), 3.54-3.36 (2H, m), 2.98-2.90 (2H, m), 2.36 (2H, t, J = 7.4 Hz), 2.18 (3H, s), 2.11-2.02 (2H, m), 1.77-1.34 (10H, m), 1.34-1.27 (1H, m), 1.23-1.14 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 172.2, 139.1, 136.1, 130.3, 128.6, 128.1, 127.5, 126.8, 126.3, 72.9, 68.4, 64.7, 59.5, 54.4, 40.4, 39.9, 36.5, 36.4, 33.9, 26.5, 25.2, 25.1, 24.9, 24.4; LCMS (ESI) $[M+H]^+$ 539, R_t = 1.19 min.; QC LCMS (ESI) $[M+H]^+$ 539.1, R_t = 4.09 min. The ^{1}H NMR and ^{13}C NMR spectra for the title compound are shown in FIGURE 6A and 6B respectively.

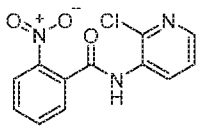
Synthetic Scheme of Example 7: 6-((11-(2-(4-Methylpiperazin-1-yl)acetyl)-11*H*-benzo[e]pyrido[3,2-b][1,4]diazepin-6-yl)oxy)hexyl nitrate





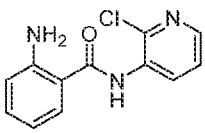
2-Nitrobenzoyl chloride

To a solution of 2-nitrobenzoic acid (5 g, 29.9 mmol) in DCM (140 mL) was added 1 drop of DMF followed by oxalyl chloride (3.7 mL, 41.9 mmol) causing effervescence. The reaction was stirred at RT for 20 min. The reaction mixture was concentrated *in vacuo* to give the title compound as a straw coloured oil (5.55 g, quant.). Material was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13-8.07 (1H, m), 7.84-7.68 (3H, m).



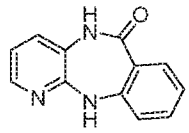
***N*-(2-Chloropyridin-3-yl)-2-nitrobenzamide**

To a solution of 2-nitrobenzoyl chloride (5.55 g, 29.9 mmol) in THF (120 mL) was added pyridine (14.5 mL, 0.18 mol) and 3-amino-2-chloropyridine (4.23 g, 32.9 mmol) causing a precipitate to form. The reaction stirred at RT for 2 h before being diluted with 10% aq citric acid and extracted with ethyl acetate. The combined organic fractions were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the product as a buff coloured solid (8.6 g, quant.). Material was used without purification. ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.61 (1H, s), 8.31 (1H, dd, J = 4.3, 1.5 Hz), 8.25-8.16 (2H, m), 7.94-7.87 (1H, m), 7.84-7.75 (2H, m), 7.54 (1H, dd, J = 8.3, 4.3 Hz).



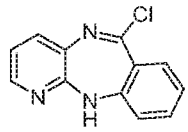
2-Amino-*N*-(2-chloropyridin-3-yl)benzamide

To a solution of *N*-(2-chloropyridin-3-yl)-2-nitrobenzamide (8.3 g, 29.9 mmol) in ethanol (100 mL) was added water (20 mL), iron (2.67 g, 47.8 mmol) and ammonium chloride (16 g, 0.3 mol). The mixture was heated at reflux for 40 min then diluted with water and filtered. The filtrate was extracted with ethyl acetate, the combined organic fractions washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title product as a beige solid (7.4 g, quant.). Material was used without purification. ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.93 (1H, s), 8.29 (1H, dd, J = 4.7, 1.8 Hz), 8.05 (1H, dd, J = 7.9, 1.8 Hz), 7.73 (1H, dd, J = 8.0, 1.5 Hz), 7.48 (1H, dd, J = 7.8, 4.7 Hz), 7.24 (1H, ddd, J = 8.4, 7.1, 1.5 Hz), 6.78 (1H, dd, J = 8.3, 0.9 Hz), 6.61 (1H, ddd, J = 8.1, 7.2, 1.1 Hz), 6.48 (2H, br s).



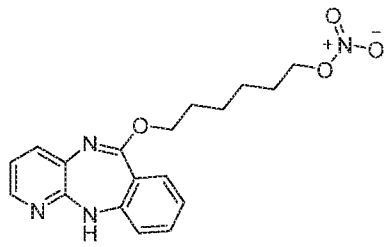
5,11-Dihydro-6*H*-benzo[e]pyrido[3,2-b][1,4]diazepin-6-one

2-Amino-*N*-(2-chloropyridin-3-yl)benzamide (3.5 g, 14.1 mmol) was heated at 210°C for 5 min. Upon reaching 200°C the reaction mixture turned black and effervescence was observed. The reaction mixture was cooled to room temperature and the solid residue washed with sat. aq. $NaHCO_3$ solution then DCM to give the title product as grey solid (2.89 g, 96%). Material was used without purification.^{1}H NMR (400 MHz, d_6-DMSO): δ 9.94 (1H, s), 8.63 (1H, s), 7.90 (1H, dd, J = 4.84, 1.6 Hz), 7.72 (1H, dd, J = 7.9, 1.6 Hz), 7.41-7.29 (2H, m), 7.13 (1H, dd, J = 8.3, 0.8 Hz), 6.97 (1H, dd, J = 7.8, 4.8 Hz), 6.95-6.89 (1H, m).



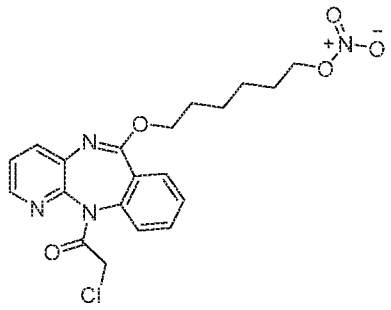
6-Chloro-11*H*-benzo[e]pyrido[3,2-b][1,4]diazepine

A mixture of 5,11-dihydro-6*H*-benzo[e]pyrido[3,2-b][1,4]diazepin-6-one (500 mg, 2.37 mmol) and phosphorus pentachloride in chlorobenzene (12 mL) was heated at 100°C for 4 h. The reaction mixture was cooled to ~4°C, isohexane (10 mL) added and solids filtered off. The solid was washed with further isohexane (10 mL) and dried *in vacuo* to give the product as a yellow solid (520 mg, 95%). Material was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (1H, s), 7.72-7.59 (3H, m), 7.41 (1H, td, J = 8.0, 1.3 Hz), 7.16-7.04 (3H, m).



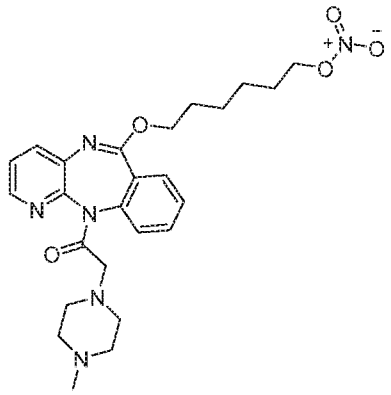
6-((11*H*-Benzo[e]pyrido[3,2-b][1,4]diazepin-6-yl)oxy)hexyl nitrate

6-Chloro-11*H*-benzo[e]pyrido[3,2-b][1,4]diazepine (500 mg, 2.37 mmol) was added to a stirred solution of 6-hydroxyhexyl nitrate (739 mg, 4.53 mmol) in DCM (2 mL) at RT. The reaction mixture was warmed to 30°C for 30 min and then partitioned between H_2O and DCM. DCM extracts were washed with saturated brine, dried (Na_2SO_4), filtered and evaporated. Crude product was purified on a silica cartridge (25 g) using a gradient of EtOAc - isohexane (0 – 60%) to give the product as a yellow residue (136 mg, 17%). ^{1}H NMR (400 MHz, d^6-DMSO): δ 7.85 (1H, dd, J = 4, 2.1 Hz), 7.48 (1H, dd, J = 7.7, 1.8 Hz), 7.36-7.26 (2H, m), 6.97-6.87 (2H, m), 6.75-6.68 (1H, m), 5.91 (1H, s), 4.46 (2H, t, J = 6.8 Hz), 4.34 (1H, t, J = 6.8 Hz), 1.87-1.73 (4H, m), 1.65-1.45 (4H, m).



6-((11-(2-Chloroacetyl)-11*H*-benzo[e]pyrido[3,2-b][1,4]diazepin-6-yl)oxy)hexyl nitrate

A stirred solution of 6-((11*H*-benzo[e]pyrido[3,2-b][1,4]diazepin-6-yl)oxy)hexyl nitrate (89 mg, 0.25 mmol), pyridine (40 µL, 0.50 mmol) and chloroacetyl chloride (40 □L, 0.50 mmol) in THF (4 mL) was heated at 70°C for 4 h. The reaction mixture was partitioned between aqueous $NaHCO_3$ and EtOAc. EtOAc extracts were washed with saturated brine, dried (Na_2SO_4), filtered and evaporated to give crude product as a yellow residue (190 mg). Material was used without purification.



6-((11-(2-(4-Methylpiperazin-1-yl)acetyl)-11*H*-benzo[e]pyrido[3,2-b][1,4]diazepin-6-yl)oxy)hexyl nitrate

A stirred solution of crude 6-((11-(2-chloroacetyl)-11*H*-benzo[e]pyrido[3,2-b][1,4]diazepin-6-yl)oxy) hexyl nitrate (190 mg, 0.43 mmol) and 1-methyl piperazine (0.24 mL,

2.19 mmol) in THF (4 mL) was heated at 60°C for 1 h. The reaction mixture was warmed to 30°C for 30 min and then partitioned between dilute aqueous $NaHCO_3$ and EtOAc. EtOAc extracts were washed with saturated brine, dried (Na_2SO_4), filtered and evaporated. Crude product was purified by MDAP to give the product as a formate salt as a yellow gum (92 mg, 42%). ^{1}H NMR (400 MHz, d^6-DMSO): δ 8.41 (1H, s, HCO_2), 8.22 (1H, d, J = 3.4 Hz), 7.67 (1H, d, J = 7.7 Hz), 7.64-7.55 (3H, m), 7.39 (1H, t, J = 7.4 Hz), 7.32-7.27 (1H, m), 4.54-4.43 (3H, m), 4.33-4.22 (1H, m), 3.48-3.27 (2H, m), 2.90-2.34 (11H, m), 1.92-1.74 (4H, m), 1.62-1.46 (4H, m); QC LCMS (ESI) $[M+H]^+$ 497.4. The ^{1}H NMR and ^{13}C NMR spectra for the title compound are shown in FIGURE 7A and 7B respectively.

The compounds of the present invention may be incorporated in various formulations for delivery. For example, topical formulations can be used and can include ophthalmically acceptable preservatives, surfactants, viscosity enhancers, buffers, sodium chloride, and water to form aqueous ophthalmically compatible solutions and suspensions. Systemic formulations (for example, orally ingested tablets) and formulations for intraocular injection are also contemplated.

The specific type of formulation selected will depend on various factors, such as the compound or its salt being used, the dosage frequency, and the location of the disease being treated. Topical ophthalmically compatible aqueous solutions, suspensions, ointments, and gels are the preferred dosage forms for the treatment of ocular diseases in the front of the eye (the cornea, iris, trabecular meshwork); or ocular diseases of the back of the eye if the compound can be formulated such that it can be delivered topically and is able to penetrate the tissues in the front of the eye. A compound according to formula (I) will normally be contained in these formulations in an amount from about 0.01 to about 10.0 weight/percent. Preferable concentrations for topical administration range from about 0.1 to about 5.0 weight/percent. Thus, for topical administration, these formulations are delivered to the surface of the eye one to six times a day, depending on the routine discretion of the skilled clinician. Systemic administration, for example, in the form of tablets is useful for the treatment of ocular disease particularly of the back of the eye, for example, the retina.

The compounds of the present invention are preferably incorporated into ophthalmically compatible formulations for delivery to the eye. The compounds may be combined with ophthalmically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmically acceptable surfactant to assist in dissolving the compound. Furthermore, the ophthalmic solution may contain an agent to increase viscosity such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle such as mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the compound in a hydrophilic base prepared from the combination of, for example, carbopol-974, or the like, according to the published formulations for analogous ophthalmic formulations; preservatives and tonicity agents can be incorporated.

The pharmaceutical compositions may include one or more buffering agent(s) or pH adjusting agent(s) to provide improved pH control. In certain topical embodiments, a pharmaceutical composition of the invention has a pH between 5.0 and 8.0, between 5.0 and 7.0, between 6.0 and 8.0, or between 6.0 and 7.0. In one embodiment, the pH of a pharmaceutical composition of the invention is about 6.3 to about 7.3. In a specific embodiment, an aqueous pharmaceutical composition of the invention has an approximately neutral pH of about 6.8.

Other contemplated excipients, which may be utilized in the pharmaceutical compositions of the invention include, for example, antimicrobial agents, antioxidants, antistatic agents, lipids such as phospholipids or fatty acids, steroids such as cholesterol, protein excipients such as serum albumin (human serum albumin), recombinant human albumin, gelatin, casein, salt-forming counterions such sodium and the like. These and additional known pharmaceutical excipients and/or additives suitable for use in the formulations of the invention are known in the art, e.g., as listed in "The Handbook of Pharmaceutical Excipients, 4th edition, Rowe et al., Eds., American

Pharmaceuticals Association (2003); and Remington: the Science and Practice of Pharmacy, 21st edition, Gennaro, Ed., Lippincott Williams & Wilkins (2005).

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In a further embodiment, the composition comprises at least two pharmaceutically acceptable carriers, such as those described herein. For purposes of the present invention, unless designated otherwise, solvates and hydrates are generally considered compositions. Preferably, pharmaceutically acceptable carriers are sterile. The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration, and rectal administration, etc. In addition, the pharmaceutical compositions of the present invention can be made up in a solid form (including without limitation capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including without limitation solutions, suspensions or emulsions). The pharmaceutical compositions can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers and buffers, etc.

In another embodiment of the present invention, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with one or more of:

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and

e) absorbents, colorants, flavors and sweeteners.

Tablets may be either film coated or enteric coated according to methods known in the art.

The pharmaceutical compositions of the invention may include an additional therapeutic agent in addition to compounds of the present invention. Further therapeutic agents may include, for instance, other compounds and antibodies useful for treating ocular diseases.

Pharmaceutical compositions of the invention can be administered to a patient. As used herein, the term "subject" or "patient" refers to human and non-human mammals, including but, not limited to, primates, rabbits, pigs, horses, dogs, cats, sheep, and cows. Preferably, a subject or patient is a human.

Various delivery methods for administration of the pharmaceutical compositions are contemplated and may include, for example, topical, intravitreal, oral, IV, intracameral, and other methods known to those of skill in the art.

In one embodiment, administration will typically be via a syringe. Thus the invention provides a delivery device (e.g. a syringe) including a pharmaceutical composition of the invention (e.g., pre-filled syringe). Patients will receive an effective amount of a compound according to formula (I) as the principal active ingredient.

In yet another embodiment, ocular inserts or films are used to deliver a compound of the present invention. In one such embodiment, a compound of formula (I) is formulated in a polymeric ocular insert comprising one or more mucoadhesive polymers that are biocompatible with the ocular surface and tear film of the eye. In certain embodiments, upon insertion of the polymeric eye insert in the cul-de-sac of the eye, the thickness of the tear film may increase for at least 30 minutes post-insertion. The one or more mucoadhesive polymers may be selected from the group comprising: hyaluronic acid (in acid or salt form), hydroxypropylmethylcellulose (HPMC), methylcellulose, tamarind seed polysaccharide (TSP), guar, hydroxypropyl guar (HP guar), scleroglucan poloxamer, poly(galacturonic) acid, sodium alginate, pectin, xanthan gum, xyloglucan gum, chitosan, sodium carboxymethylcellulose, polyvinyl alcohol, polyvinyl pyrrolidine, carbomer, polyacrylic acid and combinations thereof. In an embodiment of the present disclosure, the one or more mucoadhesive polymers may be HP guar, hyaluronic acid, and sodium hyaluronate.

The invention further provides a method for delivering a compound according to formula (I) to a patient, comprising a step of administering to the patient a pharmaceutical composition of the invention one or more times daily.

As used herein, all percentages are percentages by weight, unless stated otherwise. Unless otherwise indicated, the terms "a" and "an" are taken to mean "one", "at least one" or "one or more". Unless otherwise required by context, singular terms used herein shall include pluralities and plural terms shall include the singular. For clarity, the contents of any patents, patent applications, and references cited throughout this specification are hereby incorporated by reference in their entireties.

FORMULATION EXAMPLES

The following examples are included to demonstrate embodiments of the present invention. Those of skill in the art will appreciate that changes to the specific embodiments described herein can be made and still obtain a like result without departing from the spirit and scope of the invention.

FORMULATION EXAMPLE 1 – Topical Ophthalmic Preparation

Ingredients	Concentration (w/v %)
Compound of formula (I) or formula (II)	0.01 – 2%
Hydroxypropyl methylcellulose	0.5%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%

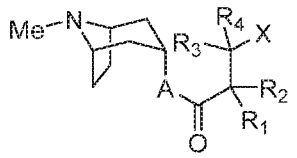
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

The present invention and its embodiments have been described in detail. However, the scope of the present invention is not intended to be limited to the particular embodiments of any process, manufacture, composition of matter, compounds, means, methods, and/or steps described in the specification. Various modifications, substitutions, and variations can be made to the disclosed material without departing from the spirit and/or essential characteristics of the present invention. Accordingly, one of ordinary skill in the art will readily appreciate from the disclosure that later modifications, substitutions, and/or variations performing substantially the same function or achieving substantially the same result as embodiments described herein may be utilized according to such related embodiments of the present invention. Thus, the following claims are intended to encompass within their scope modifications, substitutions, and variations to processes, manufactures, compositions of matter, compounds, means, methods, and/or steps disclosed herein. The claims should not be read as limited to the described order or elements unless stated to that effect. It should be understood that various changes in form and detail may be made without departing from the scope of the appended claims.

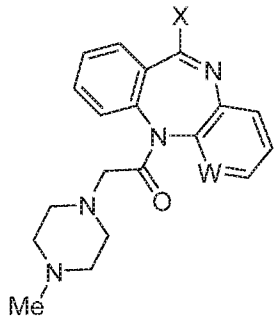
CLAIMS

What is claimed is:

1. A compound of formula (I) or formula (II):



(I)



(II)

wherein

Me = CH_3;

A = O or NR_5;

W = N or CH;

R^1 and R^2 are independently substituted as H, D, hydroxyl, alkoxy, nitrile, halogen atoms, C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl groups optionally substituted with halogen atoms; or

R^1 and R^2 are independently substituted as phenyl or benzyl groups being optionally substituted with one or more substituents selected form C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl groups, halo alkyl groups, hydroxyl, alkoxy, nitrile, nitro, amino, amide, ester, sulfone, sulfoxide, sulfonamide, and halogen atoms; or

R^1 and R^2 are independently substituted with a heterocyclic saturated, unsaturated or aromatic 5- or 6-member ring containing one or more heteroatoms selected from nitrogen, oxygen and sulfur and being optionally substituted with one or more

substituents selected form C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl, halo alkyl groups, hydroxyl, alkoxy, nitrile, nitro, amino, amide, ester, sulfone, sulfoxide or halogen atoms;

R^3 and R^4 are independently substituted with hydrogen, C_1–C_{10} straight or branched or cyclo alkyl or halo alkyl groups or

R^3 and R^4 can combine to form 3- to 6-membered rings;

R^5 = H or C_1–C_{20}, preferably C_1–C_{10}, straight or branched alkyl groups, C_1–C_{10} straight or branched haloalkyl groups;

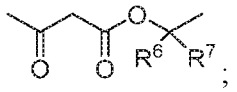
X =–ONO_2, –O–Y–Z, –S–Y–Z, or –NR_5–Y–Z;

Y is a bivalent radical having the following meaning:

a) Straight or branched C_1 – C_{20} alkyl, preferably C_1 – C_{10}, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxyl, and –ONO_2;

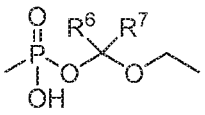
b) –C(O) (C_1 – C_{10} alkyl) – or –C(O)$(CH_2)_n$C(O)O –(C_1 – C_{10} alkyl) – or –(C_1–C_{10} alkyl) –;

c)



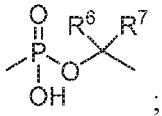
;

d)



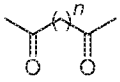
;

e)



; or

f)



wherein *n* is an integer from 0 to 20;

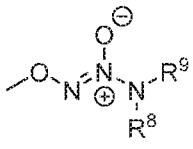
R^6 and R^7 are independently H or C_1–C_{10}, straight or branched alkyl groups, C_1–C_{10} straight or branched haloalkyl groups ; or

R^6 and R^7 can combine to form 3- to 6-membered rings; and

Z is a monovalent radical having the following meaning:

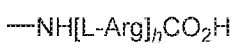
a)

b)



; or

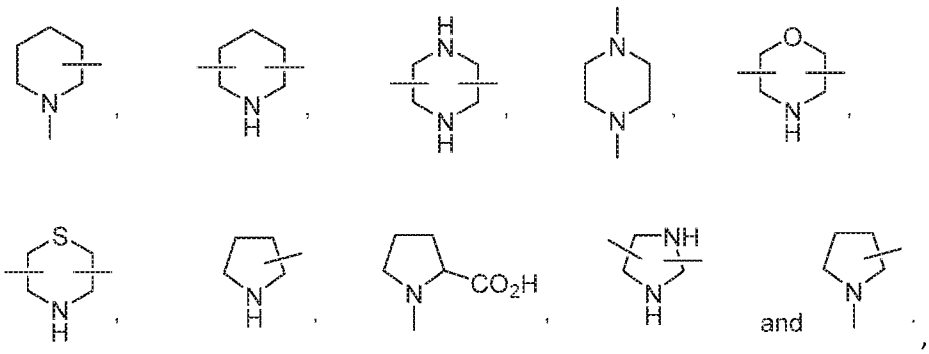
c)



wherein *h* is an integer from 0 to 10;

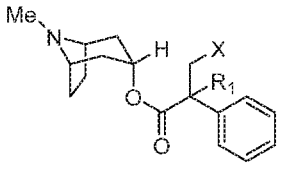
R^8 and R^9 are independently substituted as C_1 – C_{20} alkyl, preferably C_1 – C_{10}, being optionally substituted with one or more substituents selected from hydroxyl, amino, ester, carboxylic acid, and halogen atoms; or

R^8 and R^9 can combine to form 3- to 6-membered rings containing one or more heteroatoms which are selected from the group consisting of:



or a pharmaceutically acceptable salt or non-salt thereof.

2. The compound of formula (I) according to claim 1, having formula (IA):



(IA)

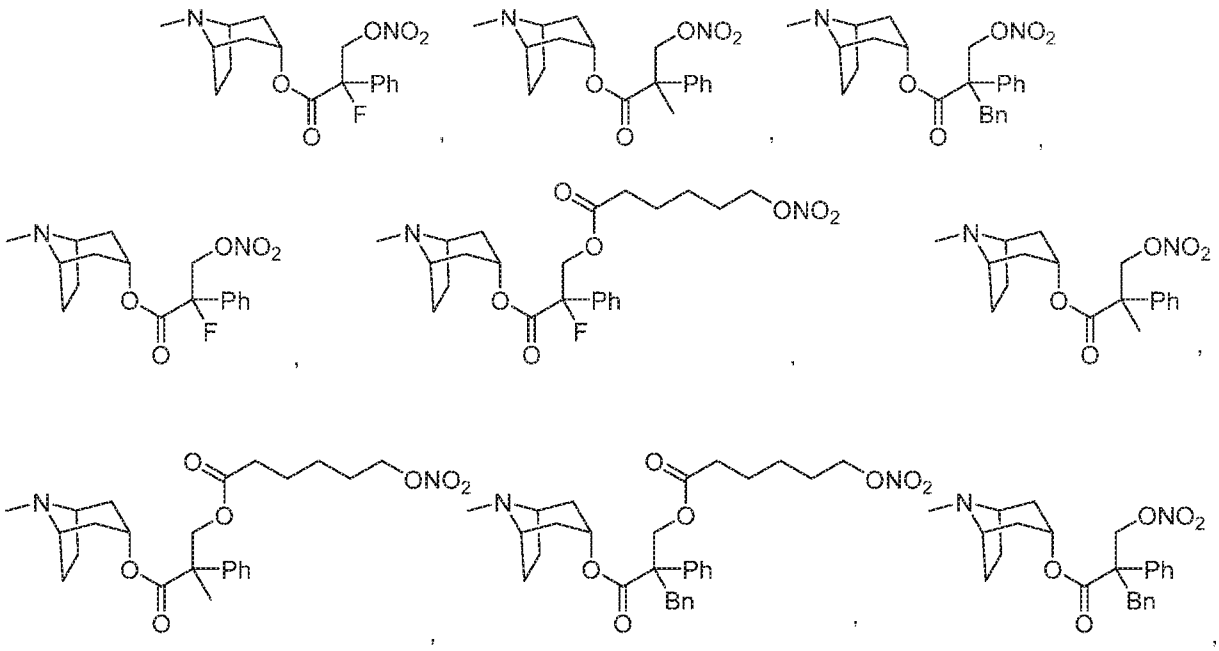
wherein R^1 = H, D, OH, halogen, $C_1 - C_{10}$ straight or branched alkyl, phenyl or benzyl, a heterocyclic saturated, unsaturated or aromatic 5- or 6-member ring, containing one or more heteroatoms selected from nitrogen, oxygen and sulfur;

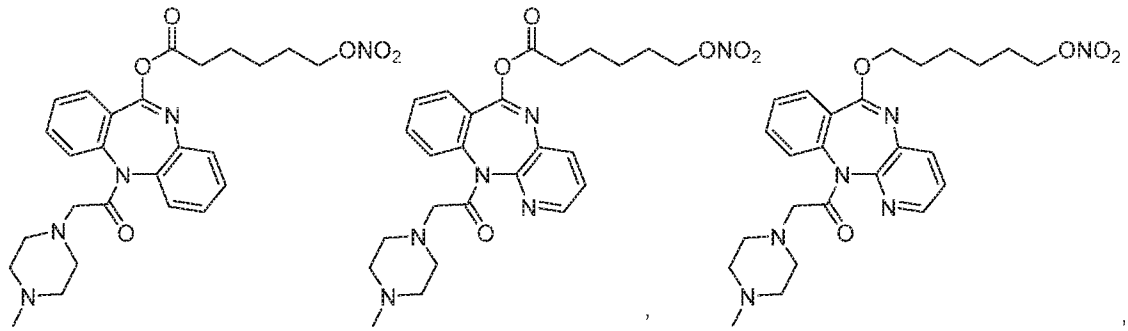
W = N or CH;

X = $–ONO_2$, –O–Y–Z, –S–Y–Z, or $–NR_5–Y–Z$;

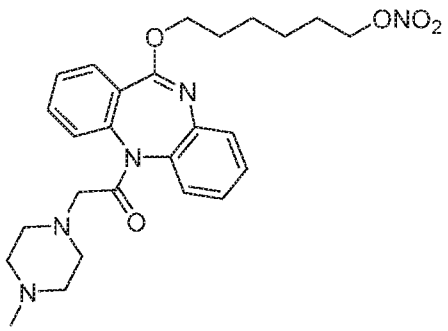
and Y and Z are as defined for claim 1.

3. A compound according to claim 1 or claim 2 or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of:





and



4. A compound according to any one of claims 1-3 or a pharmaceutically acceptable salt thereof which is selected from the group consisting of:
(*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-fluoro-3-(nitrooxy)-2-phenylpropanoate,
2-Fluoro-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl 6-(nitrooxy)hexanoate,
(*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-methyl-3-(nitrooxy)-2-phenylpropanoate,
2-Methyl-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl-6-(nitrooxy)hexanoate,
(*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-benzyl-3-(nitrooxy)-2-phenylpropanoate,
2-Benzyl-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl-6-(nitrooxy)hexanoate,and

6-((11-(2-(4-Methylpiperazin-1-yl)acetyl)-11*H*-benzo[e]pyrido[3,2-b][1,4]diazepin-6-yl)oxy)hexyl nitrate.

5. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers

6. A combination comprising a therapeutically effective amount of the compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof and one or more therapeutically active agents.

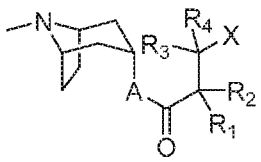
7. The composition according to claim 5, wherein said composition is an ophthalmically compatible composition.

8. The composition according to claim 7, wherein said composition is a topical composition.

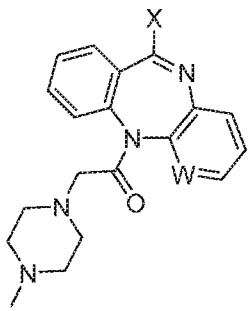
9. The composition according to claim 5, wherein said composition comprises from about 0.01 percent weight/volume to about 5 percent weight/volume of said compound.

10. The composition according to claim 5, wherein said composition is a topical composition.

11. A method of treating a mammalian subject having or at risk of having an ocular disorder, said method comprising administering to the subject an effective amount of a compound according to formula (I) or formula (II):



(I)



(II)

wherein

Me = CH_3;

A = O or NR_5;

W = N or CH;

R^1 and R^2 are independently substituted as H, D, hydroxyl, alkoxy, nitrile, halogen atoms, C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl groups optionally substituted with halogen atoms; or

R^1 and R^2 are independently substituted as phenyl or benzyl groups being optionally substituted with one or more substituents selected form C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl groups, halo alkyl groups, hydroxyl, alkoxy, nitrile, nitro, amino, amide, ester, sulfone, sulfoxide, sulfonamide, and halogen atoms; or

R^1 and R^2 are independently substituted with a heterocyclic saturated, unsaturated or aromatic 5- or 6-member ring containing one or more heteroatoms selected from nitrogen, oxygen and sulfur and being optionally substituted with one or more substituents selected form C_1–C_{20}, preferably C_1–C_{10}, straight, branched or cyclo alkyl, halo alkyl groups, hydroxyl, alkoxy, nitrile, nitro, amino, amide, ester, sulfone, sulfoxide or halogen atoms;

R^3 and R^4 are independently substituted with hydrogen, C_1–C_{10} straight or branched or cyclo alkyl or halo alkyl groups or

R^3 and R^4 can combine to form 3- to 6-membered rings;

R^5 = H or C_1–C_{20}, preferably C^1–C^{10}, straight or branched alkyl groups, C_1–C_{10} straight or branched haloalkyl groups;

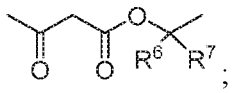
X =–ONO_2, –O–Y–Z, –S–Y–Z, or –NR_5–Y–Z;

Y is a bivalent radical having the following meaning:

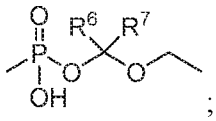
a) Straight or branched C_1 – C_{20} alkyl, preferably C_1 – C_{10}, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxyl, and –ONO_2;

b) –C(O) (C_1 – C_{10} alkyl) – or –C(O)$(CH_2)_n$C(O)O –(C_1 – C_{10} alkyl) – or –(C_1–C_{10} alkyl)–;

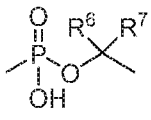
c)



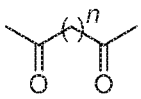
d)



e)


; or

f)



wherein *n* is an integer from 0 to 20;

R^6 and R7 are independently H or C_1–C_{10}, straight or branched alkyl groups, C_1–C_{10} straight or branched haloalkyl groups ; or

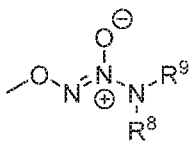
R^6 and R^7 can combine to form 3- to 6-membered rings; and

Z is a monovalent radical having the following meaning:

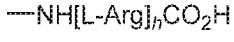
a)


;

b)


; or

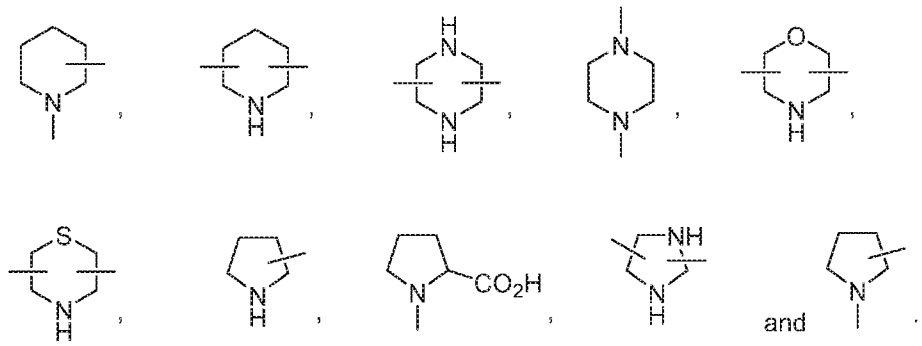
c)



wherein *h* is an integer from 0 to 10;

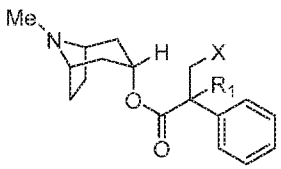
R^8 and R^9 are independently substituted as $C_1 - C_{20}$ alkyl, preferably $C_1 - C_{10}$, being optionally substituted with one or more substituents selected from hydroxyl, amino, ester, carboxylic acid, and halogen atoms; or

R^8 and R^9 can combine to form 3- to 6-membered rings containing one or more heteroatoms which are selected from the group consisting of:



or a pharmaceutically acceptable salt or non-salt thereof.

12. The method according to claim 9, wherein the compound of formula (I) has formula (IA):



(IA)

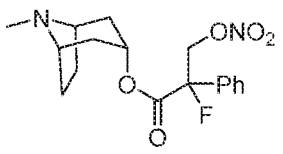
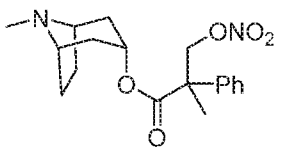
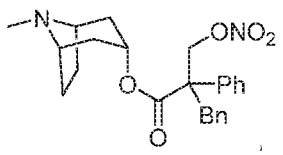
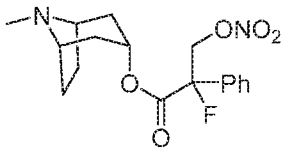
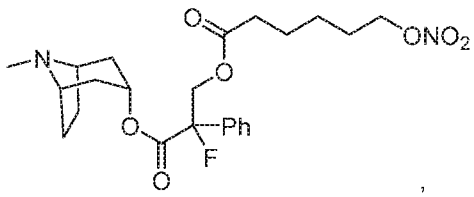
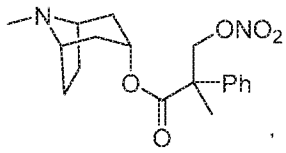
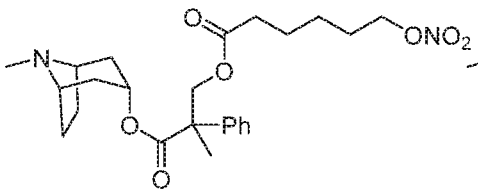
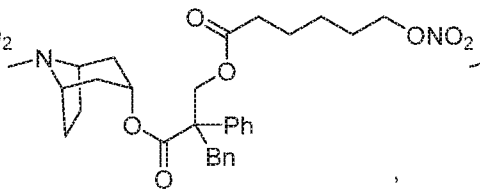
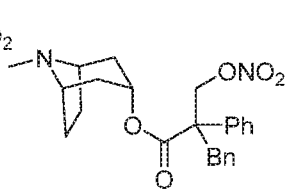
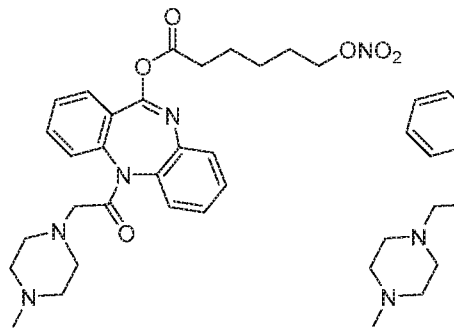
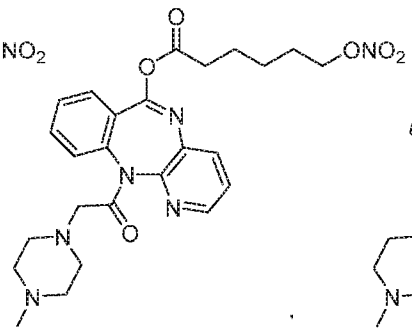
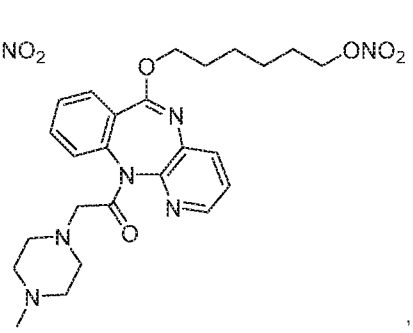
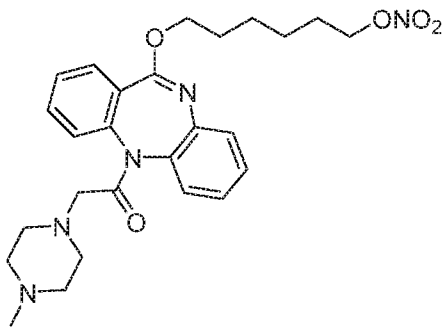
wherein R^1 = H, D, OH, halogen, straight or branched alkyl, phenyl or benzyl, a heterocyclic saturated, unsaturated or aromatic 5- or 6-member ring, containing one or more heteroatoms selected from nitrogen, oxygen and sulfur;

W = N or CH;

X = $-ONO_2$, –O–Y–Z, –S–Y–Z, or $-NR_5$–Y–Z;

and Y and Z are as defined for claim 9.

13. The method according to claim 10 or claim 11 wherein the compound of formula (I) or formula (II) is selected from the group consisting of:

, and

pharmaceutically acceptable salts thereof.

14. The method according to any one of claims 10-12 wherein the compound of formula (I) or formula (II) is selected from the group consisting of:

(*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-fluoro-3-(nitrooxy)-2-phenylpropanoate,

2-Fluoro-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl 6-(nitrooxy)hexanoate,

(*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-methyl-3-(nitrooxy)-2-phenylpropanoate,

2-Methyl-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl-6-(nitrooxy)hexanoate,

(*1R,3R,5S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-benzyl-3-(nitrooxy)-2-phenylpropanoate,

2-Benzyl-3-(((*1R,3R,5S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-3-oxo-2-phenylpropyl-6-(nitrooxy)hexanoate,

6-((11-(2-(4-Methylpiperazin-1-yl)acetyl)-11*H*-benzo[e]pyrido[3,2-b][1,4]diazepin-6-yl)oxy)hexyl nitrate, and

and pharmaceutically acceptable salts thereof.

15. The method according to any one of claims 9-11, wherein the ocular disorder is myopia.

FIGURE 1A

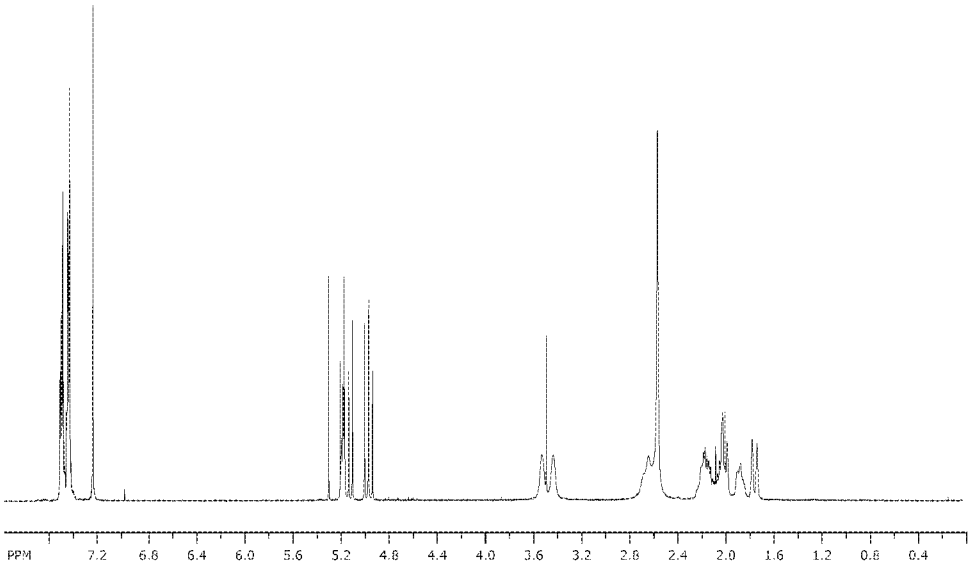


FIGURE 1B

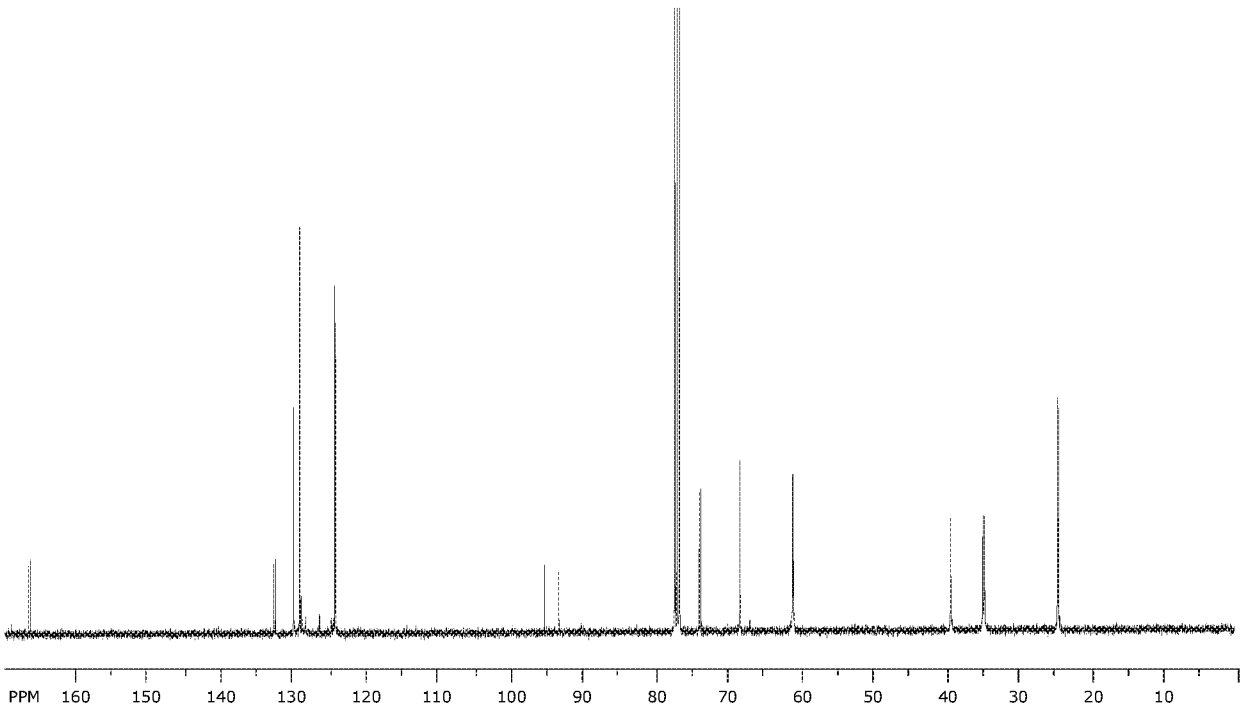


FIGURE 2A

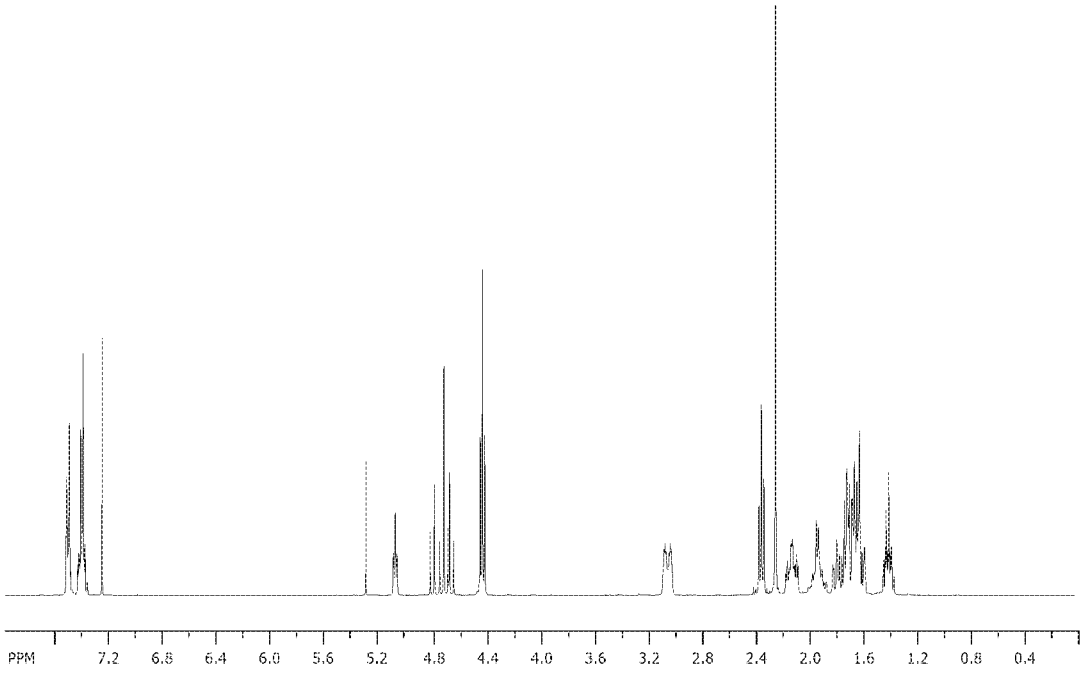


FIGURE 2B

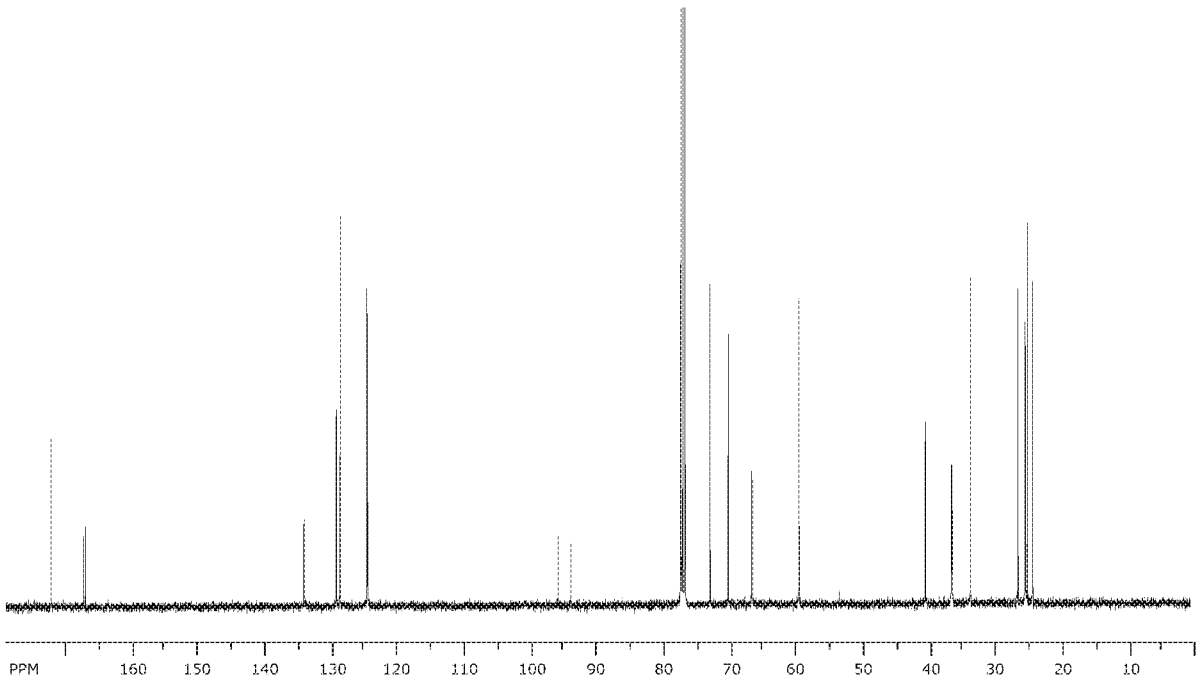


FIGURE 3A

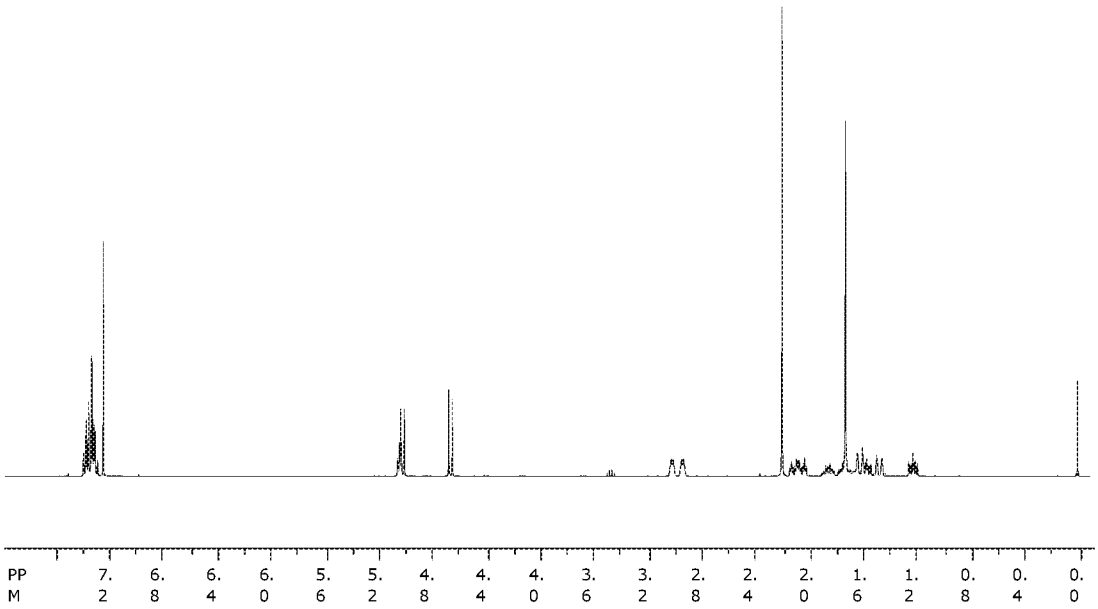


FIGURE 3B

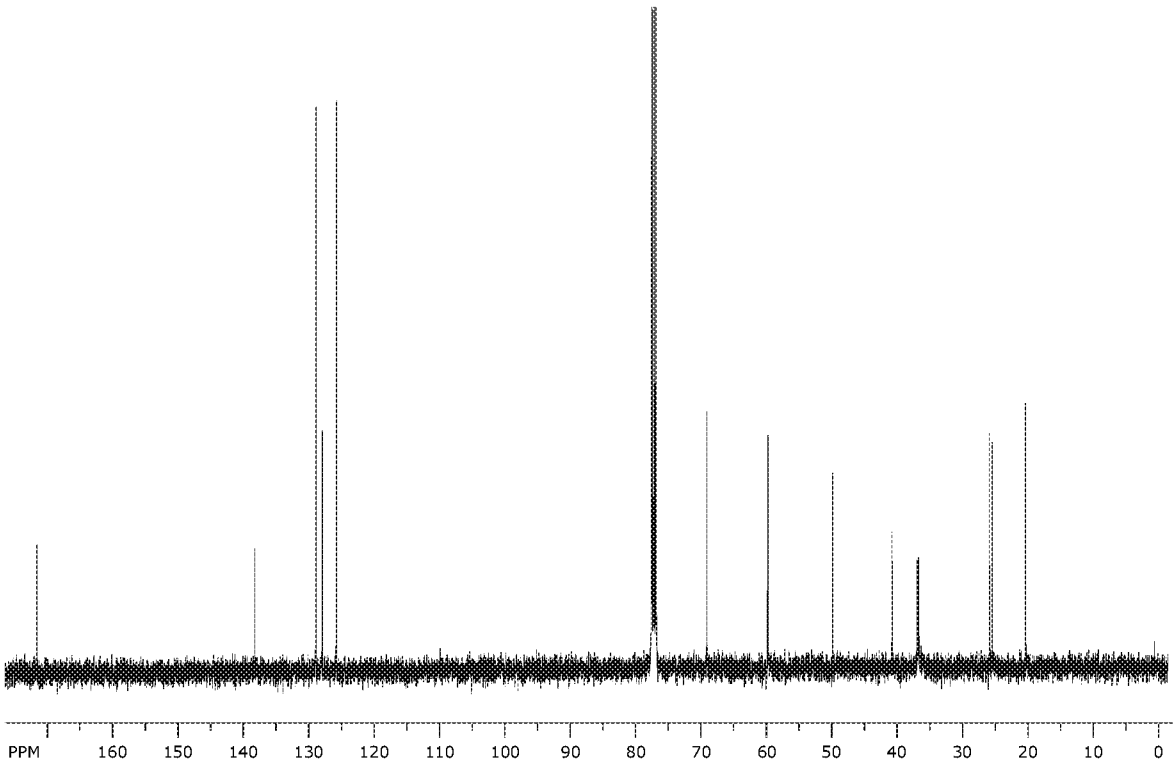


FIGURE 4A

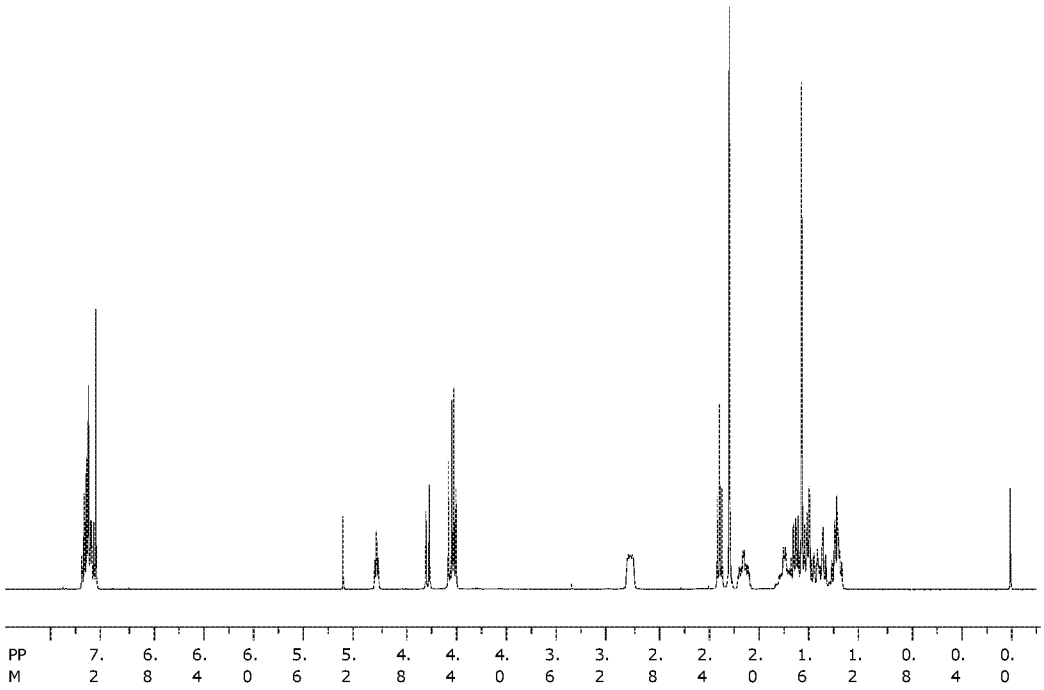


FIGURE 4B

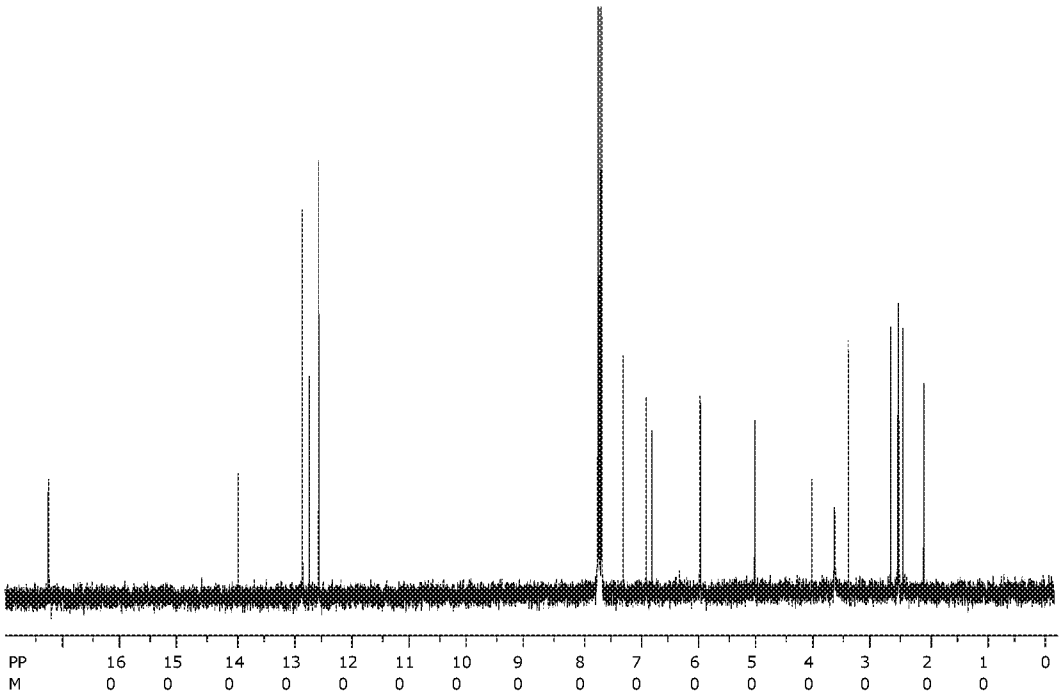


FIGURE 5A

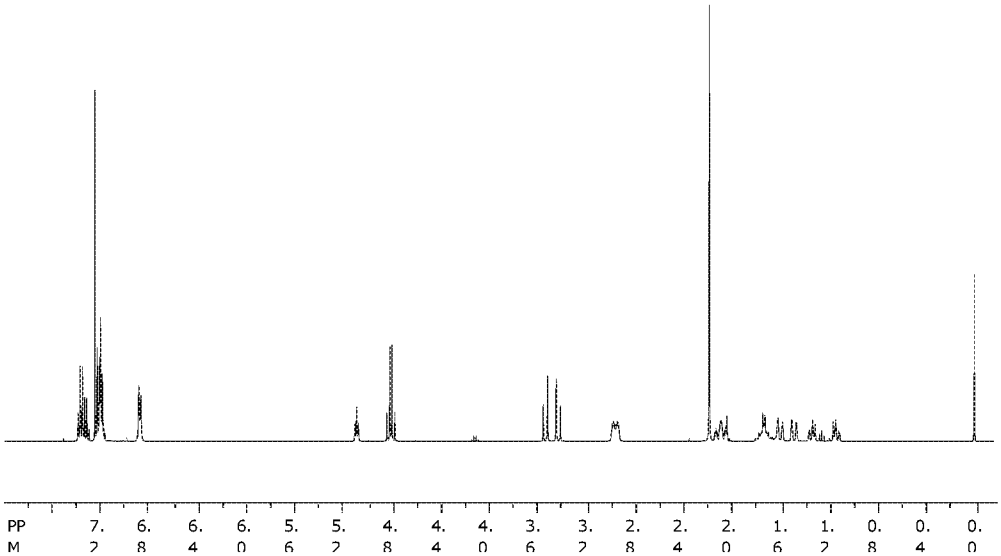
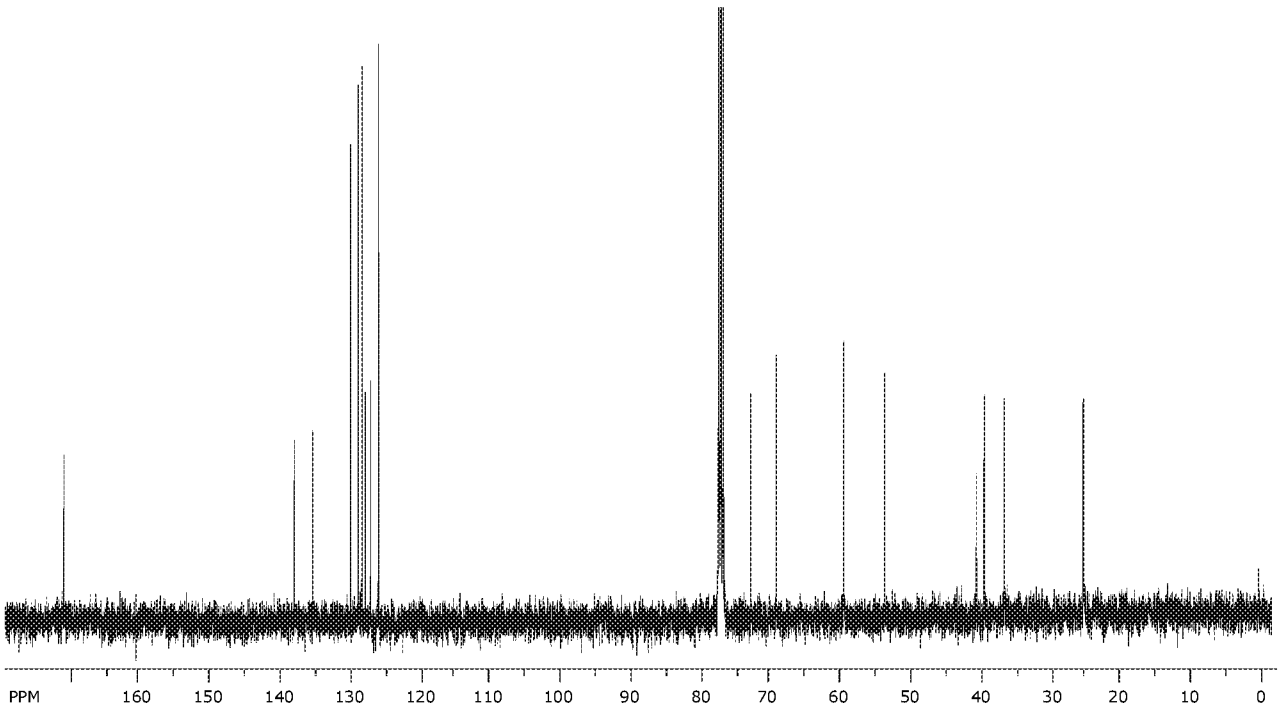


FIGURE 5B



5

FIGURE 6A

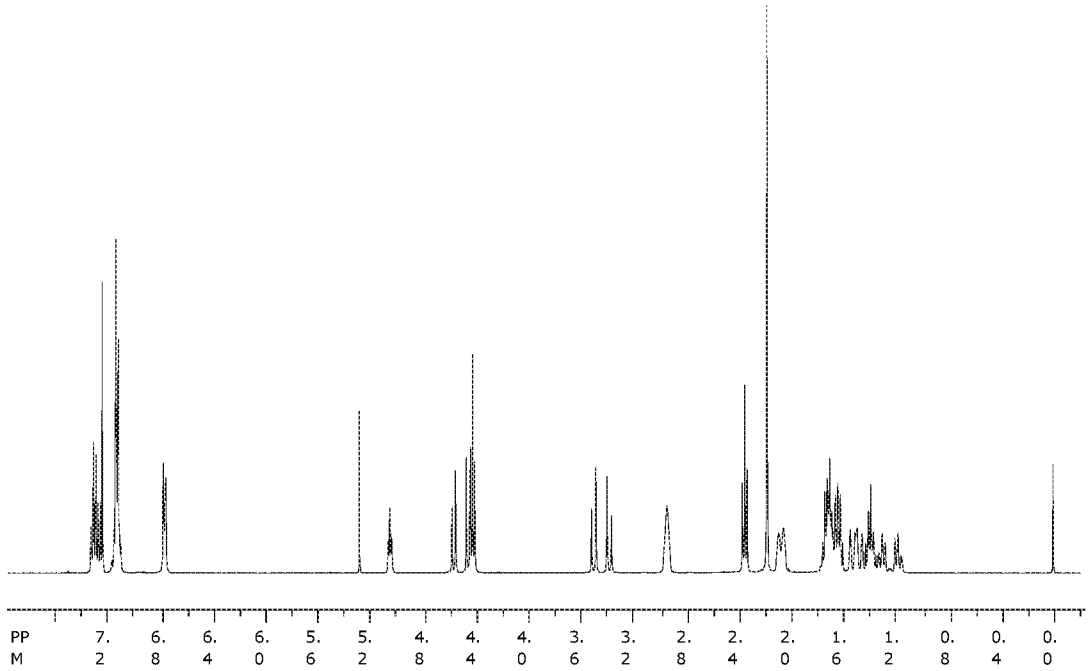


FIGURE 6B

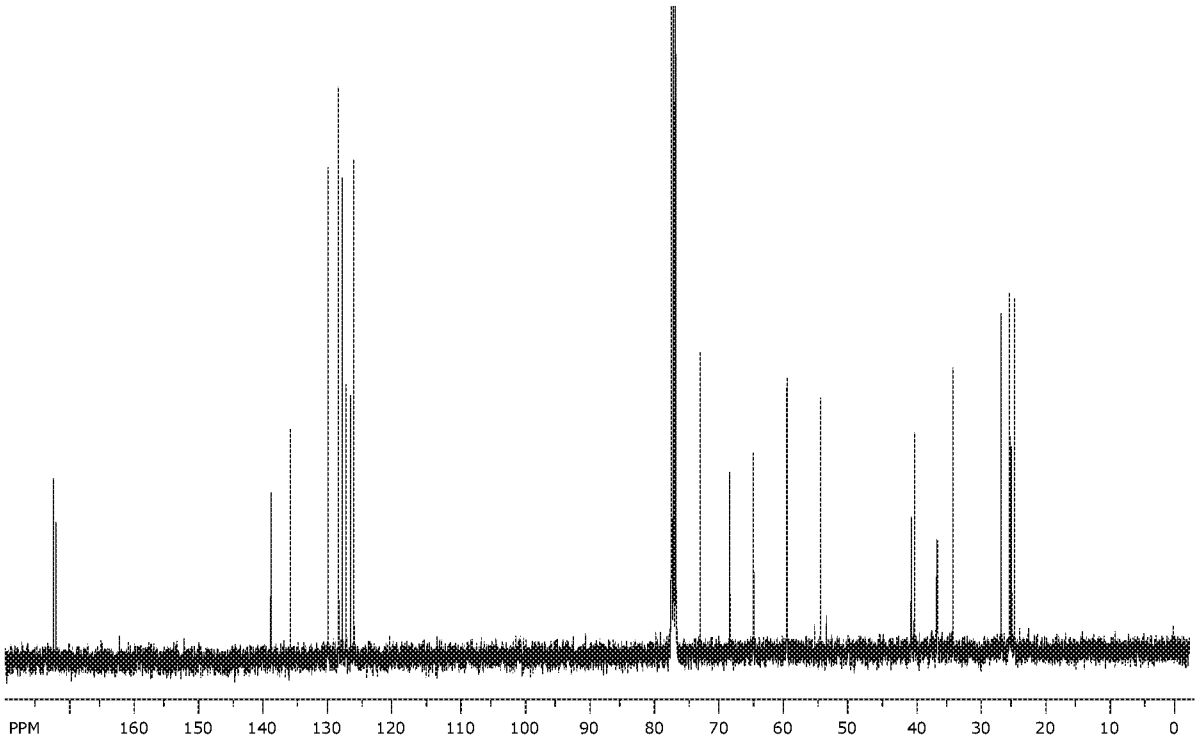


FIGURE 7A

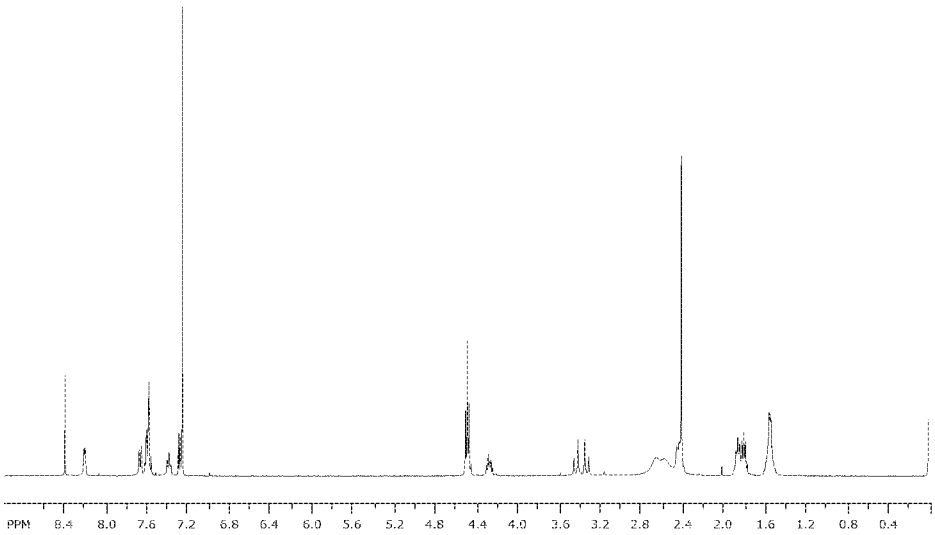
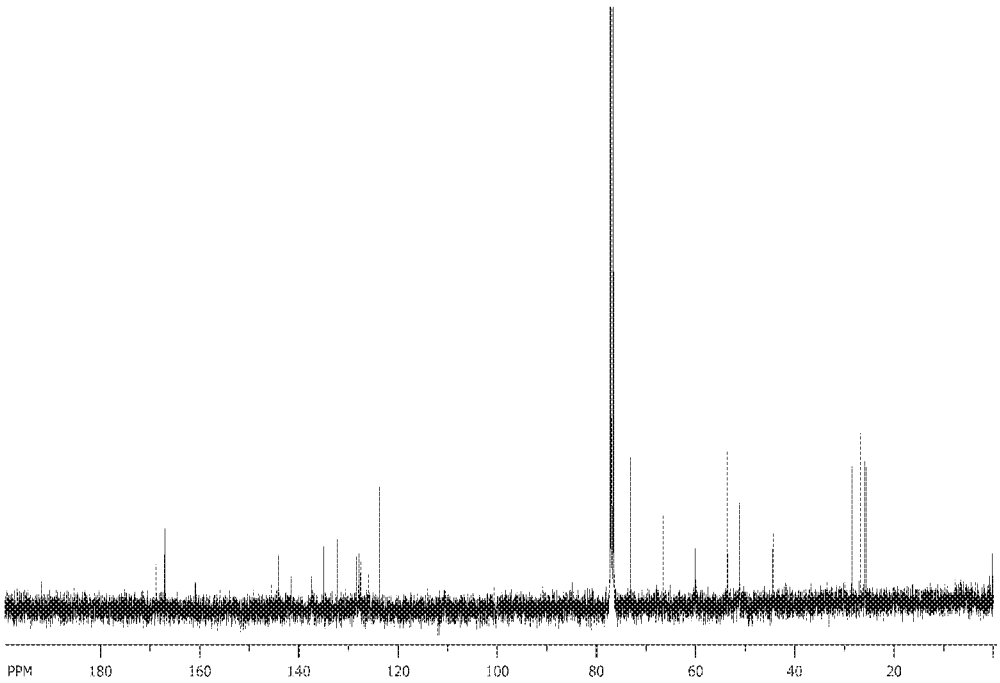


FIGURE 7B



5

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/058637

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/439 C07D471/08 A61P27/10 C07D243/14
A61K31/5513
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHWENKER G: "Zur Kenntnis der Vitalischen Farbreaktion*) I. Mitt.1 Uber fl.Eliminiernngen mit Carbanion.Zwischenstufen - [Vitali's color reaction.I. beta.-eliminations with carbanion intermediates]", ARCHIV DER PHARMAZIE UND BERICHTE DER DEUTSCHEN PHARMAZEUTISCHEN GESELLSCHAFT, VERLAG CHEMIE, WEINHEIM, DE, vol. 298, no. 12, 1965, pages 826-838, XP009509942, ISSN: 0376-0367 page 828; example V ----- -/--	1

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

[X] See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 December 2018	07/03/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fazzi, Raffaella

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/058637

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HAMMER R H ET AL: "Soft drugs-XIV. Synthesis and anticholinergic activity of soft phenylsuccinic analogs of methatropine", BIOORGANIC & MEDICINAL CHEMISTRY, PERGAMON, GB, vol. 1, no. 3, September 1993 (1993-09), pages 183-187, XP026608896, ISSN: 0968-0896, DOI: 10.1016/S0968-0896(00)82119-7 [retrieved on 1993-09-01] example 2	1-15
A	EL BAZAOUI ET AL.: "Nine new tropane derivatives alkaloids from Datura stramonium L. identified by GC/MS", FITOTERAPIA, vol. 82, 2011, pages 193-197, XP002787334, table 1	1-15
A	JR POLLING ET AL.: "Effectiveness study of atropine for progressive myopia in Europeans", EYE, vol. 30, 22 April 2016 (2016-04-22), pages 998-1004, XP002787205, page 998	1-15
A	CHUA W H ET AL: "Atropine for the Treatment of Childhood Myopia", OPHTHALMOLOGY, J. B. LIPPINCOTT CO., PHILADELPHIA, PA, US, vol. 113, no. 12, 2006, pages 2285-2291, XP027899730, ISSN: 0161-6420 [retrieved on 2006-12-01] the whole document	1-15
A	US 2007/254914 A1 (WU PEI-CHANG [TW] ET AL) 1 November 2007 (2007-11-01) claims	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2018/058637

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2007254914 A1	01-11-2007	NONE	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/058637

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

2(completely); 1, 3-15(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 2(completely); 1, 3-15(partially)

   Formula (I) of claim 1.

   ---

2. claims: 1, 3-15(all partially)

   Formula (II) of claim 1.
