TITLE OF THE INVENTION

PROSTAGLANDIN ANALOGS AS EP4 RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

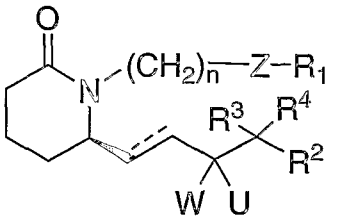
Glaucoma is a degenerative disease of the eye wherein the intraocular pressure is too high to permit normal eye function. As a result, damage may occur to the optic nerve head and result in irreversible loss of visual function. If untreated, glaucoma may eventually lead to blindness. Ocular hypertension, i.e., the condition of elevated intraocular pressure without optic nerve head damage or characteristic glaucomatous visual field defects, is now believed by the majority of ophthalmologists to represent merely the earliest phase in the onset of glaucoma.

Many of the drugs formerly used to treat glaucoma proved unsatisfactory. Current methods of treating glaucoma include using therapeutic agents such as pilocarpine, carbonic anhydrase inhibitors, beta-blockers, prostaglandins and the like. However, these therapies often produce undesirable local effects. As can be seen, there are several current therapies for treating glaucoma and elevated intraocular pressure, but the efficacy and the side effect profiles of these agents are not ideal. Therefore, there still exists the need for new and effective therapies with little or no side effects.

SUMMARY OF THE INVENTION

This invention relates to agonists of the EP4 subtype of prostaglandin E2 receptors and their use or a formulation thereof in the treatment of glaucoma and other conditions that are related to elevated intraocular pressure in the eye of a patient. In particular, this invention relates to a series of 1,6-disubstituted piperidin-2-one, 3,4-disubstituted 1,3-oxazinan-2-one, 3,4-disubstituted 1,3-thiazinan-2-one, and 4,5-disubstituted morpholin-3-one derivatives and their use to treat ocular diseases and to provide a neuroprotective effect to the eye of mammalian species, particularly humans. More particularly, this invention relates to novel EP4 agonist having the

structural formula I:



FORMULA I

or a pharmaceutically acceptable salt, enantiomer, diastereomer, prodrug or mixture thereof, wherein,

U represents H, C1-3 alkyl or is not present when W is =O;

W represents OH or =O, provided that U is not present when W is =O;

Z represents $(CH_2)_n$, or CH=CH;

R^1 represents $(CH_2)_p$hydroxy, ($(CH_2)_pCO_2R^{10}$, or $(CH_2)_n$heterocyclyl, said heterocyclyl unsubstituted or substituted with 1 to 3 groups of R^a and optionally containing an acidic hydroxyl group;

R^2 independently represents C_{1-10} alkyl, $(CH_2)_mC_{6-10}$aryl, $(CH_2)_mC_{5-10}$heterocyclyl, $(CH_2)_mC_{3-10}$ heterocycloalkyl, $(CH_2)_mC_{3-8}$ cycloalkyl, said alkyl, cycloalkyl, heterocycloalkyl, aryl or heterocyclyl unsubstituted or substituted with 1-3 groups of R^a;

R^3 and R^4 independently represent hydrogen, halogen, or C_{1-6} alkyl;

R^6 represents hydrogen, or C_{1-4} alkyl;

R^{10} represents hydrogen, C_{1-10} alkyl, C_{3-10} cyclcoalkyl, $(CH_2)_pC_{6-10}$ aryl, $(CH_2)_pC_{5-10}$ heterocyclyl;

R^a represents C_{1-6} alkoxy, C_{1-6} alkyl, CF_3, nitro, amino, cyano, C_{1-6} alkylamino, halogen, or Ra further represents for aryls and heterocyclyl, SC_{1-6}alkyl, SC_{6-10}aryl, SC_{5-10}heterocyclyl, OC_{6-10}aryl, OC_{5-10}heterocyclyl, CO_2R^6, CH_2OC_{1-6} alkyl, CH_2SC_{1-6} alkyl, CH_2Oaryl, CH_2Saryl;

--- represents a double or single bond;
p represents 0-3;
n represents 0-4; and
m represents 0-8.

This and other aspects of the invention will be realized upon inspection of the invention as a whole.

DETAILED DESCRIPTION OF THE INVENTION

The invention is described herein in detail using the terms defined below unless otherwise specified.

The term "therapeutically effective amount", as used herein, means that amount of the EP_4 receptor subtype agonist of formula I, or other actives of the present invention, that will elicit the desired therapeutic effect or response or provide the desired benefit when administered in accordance with the desired treatment regimen. A preferred therapeutically effective amount relating to the treatment of abnormal bone resorption is a bone formation, stimulating amount. Likewise, a preferred therapeutically effective amount relating to the treatment of ocular hypertension or glaucoma is an amount effective for reducing intraocular pressure and/or treating ocular hypertension and/or glaucoma.

"Pharmaceutically acceptable" as used herein, means generally suitable for administration to a mammal, including humans, from a toxicity or safety standpoint.

The term "prodrug" refers to compounds which are drug precursors which, following administration and absorption, release the claimed drug in vivo via some metabolic process. A non-limiting example of a prodrug of the compounds of this invention would be an acid of the pyrrolidinone group, where the acid functionality has a structure that makes it easily hydrolyzed after administration to a patient. Exemplary prodrugs include acetic acid derivatives that are non-narcotic, analgesics/non-steroidal, anti-inflammatory drugs having a free CH_2COOH group (which can optionally be in the form of a pharmaceutically acceptable salt, e.g.

–CH_2COO-Na+), typically attached to a ring system, preferably to an aromatic or heteroaromatic ring system.

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 10 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, cyclopentyl and cyclohexyl. When the alkyl group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group".

Cycloalkyl is a species of alkyl containing from 3 to 15 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings, which are fused. Examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

Alkoxy refers to C_1-C_6 alkyl-O-, with the alkyl group optionally substituted as described herein. Examples of alkoxy groups are methoxy, ethoxy, propoxy, butoxy and isomeric groups thereof.

Halogen (halo) refers to chlorine, fluorine, iodine or bromine.

Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and the like, as well as rings which are fused, e.g., naphthyl, phenanthrenyl and the like. An aryl group thus contains at least one ring having at least 6 atoms, with up to five such rings being present, containing up to 22 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms or suitable heteroatoms. The preferred aryl groups are phenyl, naphthyl and phenanthrenyl. Aryl groups may likewise be substituted as defined. Preferred substituted aryls include phenyl and naphthyl.

The term "heterocycloalkyl" refers to a cycloalkyl group (nonaromatic) having 3 to 10 carbon atoms in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S or N, and in which up to three additional carbon atoms may be replaced by hetero atoms.

The term "cycloalkyl" refers to a cyclic alkyl group (nonaromatic) having 3 to 10 carbon atoms.

The term "heteroatom" means O, S or N, selected on an independent basis.

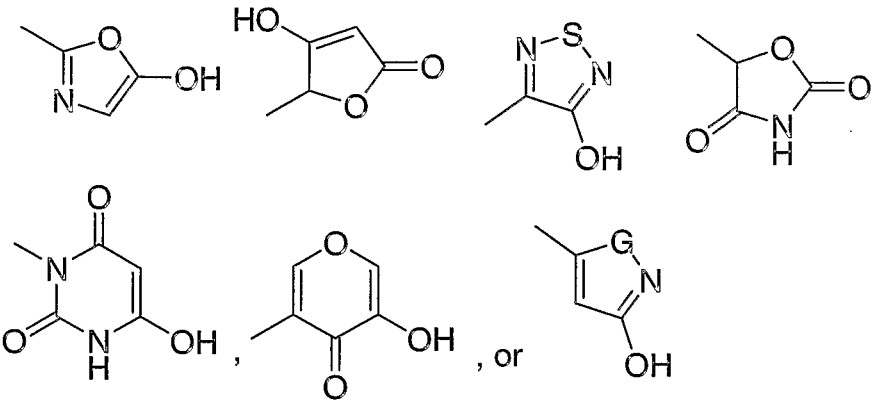
The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one or two additional carbon atoms is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen

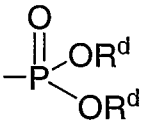
heteroatoms, said heteroaryl group being optionally substituted as described herein. Examples of this type are pyrrole, pyridine, oxazole, thiazole, tetrazole, and oxazine. For purposes of this invention the tetrazole includes all tautomeric forms. Additional nitrogen atoms may be present together with the first nitrogen and oxygen or sulfur, giving, e.g., thiadiazole.

The term heterocyclyl or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom, which results in the creation of a stable structure. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. The term heterocycle or heterocyclic includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl, and triazolyl.

For purposes of this invention, heterocyclyls containing acidic hydroxyl groups are those heterocyclyl groups that have an acidic hydroxy atom and can have a pKa in the range of 3 to 7. Non-limiting examples of heterocyclyls containing acidic hydroxyl

groups are:



G is $-C(R^c)_3$,  , $-N(R^e)_2$, O, or S and

each R^c independently is H, fluorine, cyano or C_{1-4} alkyl;
each R^d independently is H, C_{1-4} alkyl, or a pharmaceutically acceptable cation;
each R^e independently is H, $-C(=O)-R^f$, or $-SO_2R^e$, wherein R^f is C_{1-4} linear alkyl or phenyl

The term "agonist" as used herein means EP4 subtype compounds of formula I interact with the EP4 receptor to produce maximal, super maximal or submaximal effects compared to the natural agonist, PGE2. See Goodman and Gilman, The Pharmacological Basis of Therapeutics, 9th edition, 1996, chapter 2.

One embodiment of this invention is realized when R^1 is $(CH_2)_pCO_2R^{10}$, or $(CH_2)_n$heterocyclyl, said heterocyclyl unsubstituted or substituted with 1 to 3 groups of R^a and all other variables are as originally described.

Another embodiment of this invention is realized when R^1 is $(CH_2)_mC_{5-10}$heterocyclyl, said heterocyclyl unsubstituted or substituted with 1 to 3 groups of R^a and all other variables are as originally described. Another embodiment of this invention is realized when R^2 is $(CH_2)_mC_{6-10}$aryl, said aryl unsubstituted or substituted with 1 to 3 groups of R^a and all other variables are as originally described.

A sub-embodiment of this invention is realized when R^1 is $(CH_2)_pCO_2R^{10}$, or (CH_2)p-tetrazolyl said tetrazolyl unsubstituted or substituted with a R^a group and all other variables are as originally described. Still another embodiment of this invention is realized when R^2 is a phenyl unsubstituted or substituted with 1 to 3 groups of R^a and all other variables are as originally described.

Yet another embodiment of this invention is realized when R^1 is (CH_2)p-tetrazolyl and R^2 is phenyl, said tetrazolyl unsubstituted or substituted with an R^a group and phenyl is unsubstituted or substituted with 1-3 groups of R^a, and all other variables are as originally described.

Still another embodiment of this invention is realized when U is H and W is OH.

Still another embodiment of this invention is realized when U is C1-3 alkyl and W is OH.

Compounds of this invention are:

7-{(2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-6-oxopiperidin-1-yl}heptanoic acid;

isopropyl 7-{(2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-6-oxopiperidin-1-yl}heptanoate;

isopropyl (5Z)-7-{(2R)-2-[(1E,3R)-4,4-difluoro-3-hydroxy-4-phenylbut-1-en-1-yl]-6-oxopiperidin-1-yl}hept-5-enoate;

(5Z)-7-{(2R)-2-[(1E,3R)-4,4-difluoro-3-hydroxy-4-phenylbut-1-en-1-yl]-6-oxopiperidin-1-yl}hept-5-enoic acid;

7-{[(2*R*)-2-(3*R*)-3-hydroxy-4-phenyl-butyl]-6-oxo-piperdin-1-yl} heptanoic acid;

isopropyl 7-{(2*R*)-2-[(1*E*)-4,4-difluoro-3-oxo-4-phenylbut-1-enyl]-6-oxopiperidin-1-yl}heptanoate;

6-[(3*R*)-3-hydroxy-4-phenyl-butyl]-1-[6-(1*H*-tetrazol-5-yl)-hexyl]-piperidin-2-one;

(6*S*)-6-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-1-[6-(2*H*-tetraazol-5-yl)hexyl]piperazin-2-one;

(6*R*)-6-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-1-[6-(2*H*-tetraazol-5-yl)hexyl]piperidin-2-one;

7-{(2*R*)-2-[(3*R*)-4-(3-bromophenyl)-4,4-difluoro-3-hydroxybutyl]-6-oxopiperidin-1-yl}heptanoic acid;

or a pharmaceutically acceptable salt, enantiomer, diastereomer, prodrug or mixture thereof.

Another embodiment of this invention is directed to a composition containing an EP_4 agonist of Formula I and optionally a pharmaceutically acceptable carrier.

Yet another embodiment of this invention is directed to a method for decreasing elevated intraocular pressure or treating glaucoma by administration, preferably topical or intra-camaral administration, of a composition containing an EP4 agonist of Formula I and optionally a pharmaceutically acceptable carrier. Use of the compounds of formula I for the manufacture of a medicament for treating elevated intraocular pressure or glaucoma or a combination thereof is also included in this invention

This invention is further concerned with a process for making a pharmaceutical composition comprising a compound of formula I.

This invention is further concerned with a process for making a pharmaceutical composition comprising a compound of formula I, and a pharmaceutically acceptable carrier.

The claimed compounds bind strongly and act on PGE_2 receptor, particularly on the EP4 subtype receptor and therefore are useful for preventing and/or treating glaucoma and ocular hypertension.

Dry eye is a common ocular surface disease afflicting millions of people. Although it appears that dry eye may result from a number of unrelated pathogenic causes, the common end result is the breakdown of the tear film, which results in dehydration of the exposed outer surface of the eye. (Lemp, Report of the Nation Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes, The *CLAO* Journel, 21(4):221-231 (1995)). Functional EP4 receptors have been found in human conjuctival epithelial cells (see US Patent 6,344,477, incorporated by reference in its entirey) and it is appreciated that both human corneal epithelial cells (Progess in Retinal and Eye Research, 16:81-98(1997)) and conjuctival cells (Dartt et al. Localization of nerves adjacent to goblet cells in rat conjucntiva. Current Eye Research, 14:993-1000 (1995)) are capable of secreting mucins. Thus, the compounds of formula I are useful for treating dry eye.

Macular edema is swelling within the retina within the critically important central visual zone at the posterior pole of the eye: It is believed that EP4 agonist which lower IOP are useful for treating diseases of the macular such as macular edema or macular degeneration. Thus, another aspect of this invention is a method for treating macular edema or macular degeneration.

Glaucoma is characterized by progressive atrophy of the optic nerve and is frequently associated with elevated intraocular pressure (IOP). It is possible to treat glaucoma, however, without necessarily affecting IOP by using drugs that impart a neuroprotective effect. See Arch. Ophthalmol. Vol. 112, Jan 1994, pp. 37-44; Investigative Ophthamol. & Visual Science, **32**, 5, April 1991, pp. 1593-99. It is believed that EP4 agonist which lower IOP are

useful for providing a neuroprotective effect. They are also believed to be effective for increasing retinal and optic nerve head blood velocity and increasing retinal and optic nerve oxygen by lowering IOP, which when coupled together benefits optic nerve health. As a result, this invention further relates to a method for increasing retinal and optic nerve head blood velocity, or increasing retinal and optic nerve oxygen tension or providing a neuroprotective effect or a combination thereof by using an EP4 agonist of formula I.

The compounds produced in the present invention are readily combined with suitable and known pharmaceutically acceptable excipients to produce compositions which may be administered to mammals, including humans, to achieve effective IOP lowering. Thus, this invention is also concerned with compositions and methods of treating ocular hypertension, glaucoma, macular edema, macular degeneration, for increasing retinal and optic nerve head blood velocity, for increasing retinal and optic nerve oxygen tension, for providing a neuroprotective effect or for a combination thereof by administering to a patient in need thereof one of the compounds of formula I alone or in combination with one or more of the following active ingredients, a β-adrenergic blocking agent such as timolol, betaxolol, levobetaxolol, carteolol, levobunolol, a parasympathomimetic agent such as pilocarpine, a sympathomimetic agents such as epinephrine, iopidine, brimonidine, clonidine, para-aminoclonidine, a carbonic anhydrase inhibitor such as dorzolamide, acetazolamide, metazolamide or brinzolamide; COSOPT®, a Maxi-K channel blocker such as Penitrem A, paspalicine, charybdotoxin, iberiotoxin, Paxicillan, Aflitram, Verroculogen, and as disclosed in WO 03/105868 (USSN 60/389,205), WO 03/105724 (60/389,222), WO 03/105847 (60/458,981), 60/424790, filed November 8, 2002 (Attorney docket 21260PV), 60/424808, filed November 8, 2002 (Attorney docket 21281PV), 09/765716, filed January 17, 2001, 09/764738, filed January 17, 2001 and PCT publications WO 02/077168 and WO 02/02060863, all incorporated by reference in their entirety herein and in particular Maxi-K channel blockers such as 1-(1-isobutyl-6-methoxy-1H-indazol-3-yl)-2-methylpropan-1-one; 1-[1-(2,2-dimethylpropyl)-6-methoxy-1H-indazol-3-yl]-2-methylpropan-1-one; 1-[1-(cyclohexylmethyl)-6-methoxy-1H-indazol-3-yl]-2-methylpropan-1-one; 1-(1-hexyl-6-methoxy-1H-indazol-3-yl)-2-methylpropan-1-one; 1-[1-(2-ethylhexyl)-6-methoxy-1H-indazol-3-yl]-2-methylpropan-1-one; 1-(3-isobutyryl-6-methoxy-1H-indazol-1-yl)buan-2-one; 1-(3-isobutyryl-6-methoxy-1H-indazol-1-yl)-3,3-dimethylbutan-2-one; 1-(3-cyclopentylcarbonyl)-6-methoxy-1H-indazol-1-yl)-3,3-dimethylbutan-2-one; 1-(3,3-dimethyl-2-oxobutyl) -6-methoxy-1H-indazole-3-carboxylic acid; and 1-[3-(3-hydroxypropanoyl) -6-methoxy-1H-indazol-1-yl]-3,3-dimethylbutan-2-one, a prostaglandin such as latanoprost, travaprost, unoprostone, rescula, S1033 (compounds set forth in US Patent Nos. 5,889,052;

5,296,504; 5,422,368; and 5,151,444); a hypotensive lipid such as lumigan and the compounds set forth in US Patent No. 5,352,708; a neuroprotectant disclosed in US Patent No. 4,690,931, particularly eliprodil and R-eliprodil as set forth in WO 94/13275, including memantine; and/or an agonist of 5-HT2 receptors as set forth in PCT/US00/31247, particularly 1-(2-aminopropyl)-3-methyl-1H-imdazol-6-ol fumarate and 2-(3-chloro-6-methoxy-indazol-1-yl)-1-methyl-ethylamine.

Use of the compounds of formula I for the manufacture of a medicament for treating ocular hypertension, glaucoma, macular edema, macular degeneration, for increasing retinal and optic nerve head blood velocity, for increasing retinal and optic nerve oxygen tension, for providing a neuroprotective effect or for a combination thereof is also included in this invention.

The EP4 agonist used in the instant invention can be administered in a therapeutically effective amount intravaneously, subcutaneously, topically, transdermally, parenterally or any other method known to those skilled in the art. Ophthalmic pharmaceutical compositions are preferably adapted for topical administration to the eye in the form of solutions, suspensions, ointments, creams or as a solid insert. Ophthalmic formulations of this compound may contain from 0.001 to 5% and especially 0.001 to 0.1% of medicament. Higher dosages as, for example, up to about 10% or lower dosages can be employed provided the dose is effective in reducing intraocular pressure, treating glaucoma, increasing blood flow velocity or oxygen tension. For a single dose, from between 0.001 to 5.0 mg, preferably 0.005 to 2.0 mg, and especially 0.005 to 1.0 mg of the compound can be applied to the human eye.

The pharmaceutical preparation which contains the compound may be conveniently admixed with a non-toxic pharmaceutical organic carrier, or with a non-toxic pharmaceutical inorganic carrier. Typical of pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or aralkanols, vegetable oils, peanut oil, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethyl-cellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally employed acceptable carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium borate, sodium acetates, gluconate buffers, and other conventional

ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitylate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetracetic acid, and the like. Additionally, suitable ophthalmic vehicles can be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems, isotonic boric acid vehicles, isotonic sodium chloride vehicles, isotonic sodium borate vehicles and the like. The pharmaceutical preparation may also be in the form of a microparticle formulation. The pharmaceutical preparation may also be in the form of a solid insert. For example, one may use a solid water soluble polymer as the carrier for the medicament. The polymer used to form the insert may be any water soluble non-toxic polymer, for example, cellulose derivatives such as methylcellulose, sodium carboxymethyl cellulose, (hydroxyloweralkyl cellulose), hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose; acrylates such as polyacrylic acid salts, ethylacrylates, polyactylamides; natural products such as gelatin, alginates, pectins, tragacanth, karaya, chondrus, agar, acacia; the starch derivatives such as starch acetate, hydroxymethyl starch ethers, hydroxypropyl starch, as well as other synthetic derivatives such as polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl methyl ether, polyethylene oxide, neutralized carbopol and xanthan gum, gellan gum, and mixtures of said polymer.

Suitable subjects for the administration of the formulation of the present invention include primates, man and other animals, particularly man and domesticated animals such as cats, rabbits and dogs.

The pharmaceutical preparation may contain non-toxic auxiliary substances such as antibacterial components which are non-injurious in use, for example, thimerosal, benzalkonium chloride, methyl and propyl paraben, benzyldodecinium bromide, benzyl alcohol, or phenylethanol; buffering ingredients such as sodium chloride, sodium borate, sodium acetate, sodium citrate, or gluconate buffers; and other conventional ingredients such as sorbitan monolaurate, triethanolamine, polyoxyethylene sorbitan monopalmitylate, ethylenediamine tetraacetic acid, and the like.

The ophthalmic solution or suspension may be administered as often as necessary to maintain an acceptable IOP level in the eye. It is contemplated that administration to the mammalian eye will be from once up to three times daily.

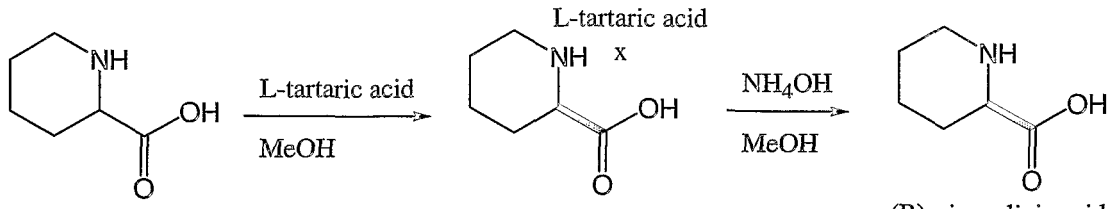
For topical ocular administration the novel formulations of this invention may take the form of solutions, gels, ointments, suspensions or solid inserts, formulated so that a unit dosage comprises a therapeutically effective amount of the active component or some multiple thereof in the case of a combination therapy.

Regarding treatment of ocular disorders, the formula I agonists generally have an EC_{50} value from about 0.001 nM to about 100 microM, although agonists with activities outside this range can be useful depending upon the dosage and route of administration. In a subclass of the present invention, the agonists have an EC_{50} value of from about 0.01 microM to about 10 microM. In a further subclass of the present invention, the agonists have an EC_{50} value of from about 0.1 microM to about 10 microM. EC_{50} is a common measure of agonist activity well known to those of ordinary skill in the art and is defined as the concentration or dose of an agonist that is needed to produce half, i.e. 50%, of the maximal effect. See also, Goodman and Gilman's, *The Pharmacologic Basis of Therapeutics*, 9th edition, 1996, chapter 2, E. M. Ross, *Pharmacodynamics, Mechanisms of Drug Action and the Relationship Between Drug Concentration and Effect*, and PCT US99/23757, filed October 12, 1999, which are incoroporated by reference herein in their entirety.

The herein examples illustrate but do not limit the claimed invention. Each of the claimed compounds are EP_4 agonists and are useful for a number of physiological ocular and bone disorders.

The compounds of this invention can be made, with some modification, in accordance with US Patent No. 6,043,275, EP0855389, WO 03/047417 (USSN 60/337228), WO 03/047513 (USSN 60/338,117), USSN 60/406,530 (Merck Docket No. MC060) and WO 01/46140, all of which are incorporated herein by reference in their entirety. The following non-limiting schemes and examples given by way of illustration is demonstrative of the present invention.

Preparative Example 1



(R)-pipecolinic acid

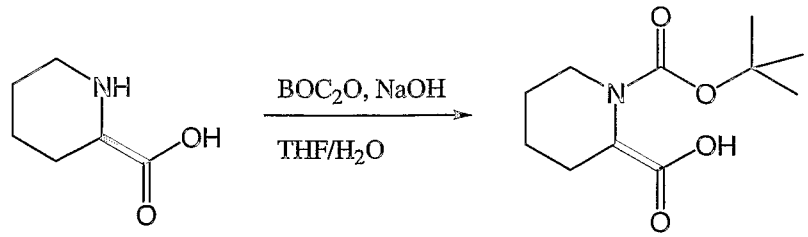
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To a slurry of (+/-)-pipecolinic acid (395 g, 3.06 moles) in MeOH (1.8L) at 60 °C was added L-tartaric acid (459 g, 3.06 moles). The slurry was warmed to reflux and aged 1h (hour). The slurry was cooled to 23 °C, filtered, and the desired (R)-pipecolinic acid/L-tartaric acid filtercake was washed with MeOH (200 mL). The filtercake was air dried a white solid was isolated. The pipecolinic acid tartrate salt typically assayed at 85-89 %ee.

A slurry of salt (383g) in 2:1 H_2O/acetone (380 mL/190 mL) was warmed to reflux (60-65 °C) until all solids had dissolved. Acetone (1330 mL) was added over 2h while maintaining a reflux. The slurry was allowed to cool to 15-20 °C over 1h and then filtered, washed with 4:1 acetone/H_2O (380 mL) and then air dried under vacuum. Isolated 313g of pipecolinic acid tartrate salt (>99 %ee).

To a slurry of (R)-pipecolinic acid tartrate salt (312g) in MeOH (3.0 L) was added 28% NH_4OH (83 mL, 1.1eq) over 0.5h. The white slurry was aged 0.5h at ambient temperature and then the ammonium tartrate precipitate was filtered off. The filtercake was rinsed with MeOH (300 mL). The combined filtrate and rinse was concentrated to a white solid of (**1**).

Preparative Example 2

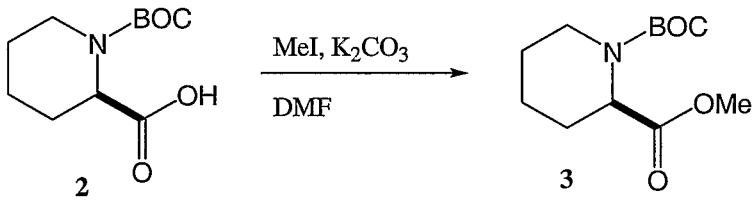


(R)-pipecolinic acid
1

2

To a slurry of pipecolinic acid (109.7 g) and BOC_2O (222.4 g) in 1:1 tetrahydrofuran (THF)/H_2O (550/550 mL) was added 50% NaOH (45 mL). The slurry was warmed to reflux and aged 5h at reflux. The solution was cooled to 23 °C and then washed with heptane (550 mL) to remove unreacted BOC_2O. The aqueous (aq.) layer was then acidified with 5N HCl (170 mL) to pH 4-5. The resulting slurry was extracted with 550 mL of tert-butyl methyl ether (MTBE). The organic layer was dried over Na_2SO_4 and then concentrated to a white solid of (**2**).

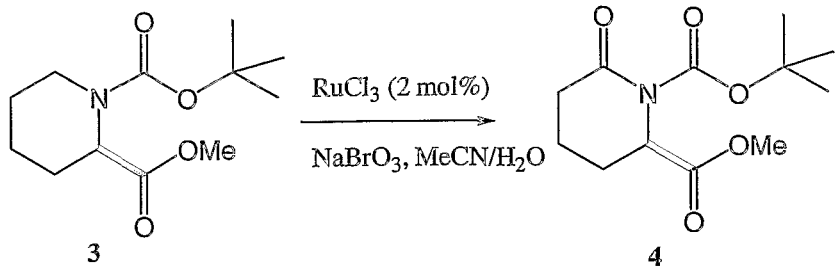
Preparative Example 3



2 3

To a solution of N-BOC-pipecolinic acid (166.5 g, 726 mmoles) in 500 mL dimethylformamide (DMF) was added MeI (123.7 g, 871 mmoles) and K_2CO_3 (100.4 g, 726 moles). The reaction mixture slowly exothermed to 40 °C after 0.5h during a 4h age period at ambient temperature. Added MTBE (830 mL) and then washed with H_2O (2 x 830mL) and 20% brine (300 mL). The organic layer was dried over Na_2SO_4 and concentrated to an oil (**3**).

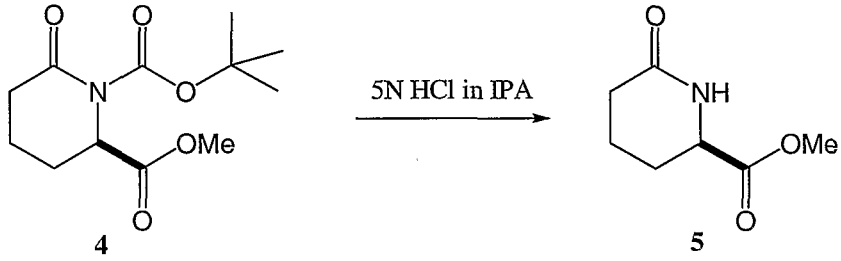
Preparative Example 4



3 4

To a solution of butoxycarbonyl (Boc)-Me ester (152.6 g, 627 mmol) in MeCN (305 mL) was added $RuCl_3$ (2.6 g, 12.5 mmol). A solution of $NaBrO_3$ (142.0 g, 941 mmol) in H_2O (760 mL) was added over 2h. The solution was aged 12h at ambient temperature. Added EtOAc (760 mL) and cut the aqueous layer. The dark organic layer was washed with 10% Na_2SO_3 (305 mL) while the organic layer turned clear and the aqueous layer turned cloudy grey. The organic layer was washed with saturated brine (150 mL) and then dried over Na_2SO_4 to give oil (**4**).

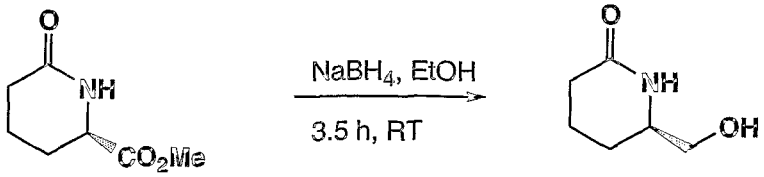
Preparative Example 5



4 5

To a solution of BOC-Lactam (135.4 g, 526 mmol) in 135 mL of isopropyl alcohol (IPA) was added 5N HCl in 263 mL/1316 mmol isopropyl alcohol (IPA) over 15min. Vigorous gas evolution occurred for 15min and then the solution was aged 2.5h at ambient temperature. Added EtOAc (800 mL) and washed with 15% Na_2CO_3 (350 mL). The aqueous layer was extracted with EtOAc (400 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to oil (**5**). The enantiomeric purity was assayed at >99 %ee.

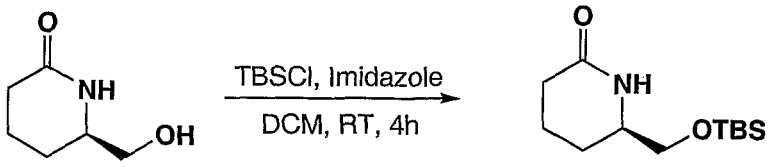
Preparative Example 6



5 6

To a solution of lactam ester (8.10 g, 51.7 mmol) in anhydrous ethanol (500 mL) was added sodium borohydride (2.5 g, 1.2 eq) in 0.5 g increments over 30 minutes. The solution was stirred for 3.5 hours at room temperature. The mixture was then treated with glacial acetic acid (2.8 equiv) and the precipitate removed by filtering through a plug of celite. The filtrate was then concentrated *in vacuo* and the resulting oil solidified upon standing under vacuum. The crude product was dissolved in CH_2Cl_2 (50 mL), treated with $KHCO_3$ (1.5 equiv), aged for 1h, filtered through a plug of Celite and the resulting filtrate was concentrated in vacuo to give the title compound **6**, which was used directly in the next step without further purification.

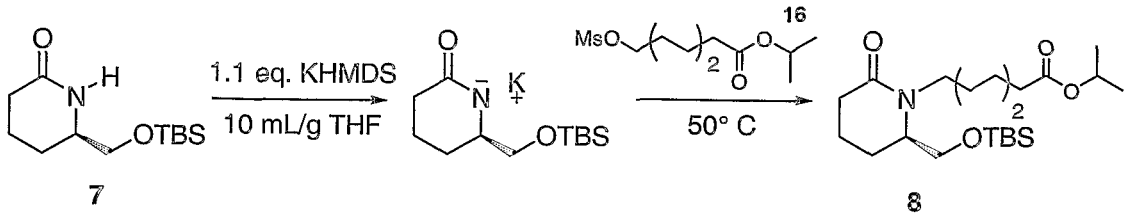
Preparative Example 7



6 7

To a solution of the lactam alcohol (10g, 77.5 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (50 mL) at 0 °C under N_2 atmosphere was added imidazole (6.9 g, 100.8 mmol, 1.3 equiv, (the amount of imidazole was adjusted to neutralize any AcOH from the previous step) and 14 g/93.0 mmol/1.2 equiv of tert-butyldimethylsilyl chloride (TBSCl). The resulting mixture was warmed to room temperature (RT) and aged for 4 hours. Once the reaction was judged complete, CH_2Cl_2 (100 mL) was added, followed by 1N HCl solution (30 mL). The organic layer was separated and the aqueous layer was back-extracted with CH_2Cl_2 (2x50 mL). The combined organic layer was washed with 20% $NaHCO_3$ solution (40 mL), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the desired compound as white solid. The silicon-containing byproducts can be removed by washing the solid with cold heptane (3mL/g) at -78 °C to give the titled compound 7.

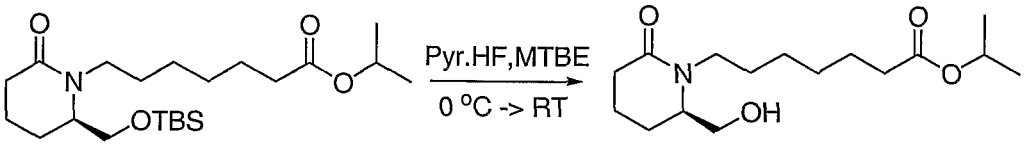
Preparative Example 8



7 8

To a 15 °C solution of lactam **7** (2.0 g, 8.22 mmoles) in THF (KF < 200 ppm) was added 1.90 g/ 9.04 mmoles of solid potassium bis[trimethylsilyl]amide (KHMDS) in 20 mL of tetrahydrofuran (THF) and aged for 10 min at room temperature (rt). Freshly prepared mesylate (0.93 g, 8.22 mmoles, KF < 800 ppm) was added to the solution as a neat oil and the reaction was heated to 50 °C and aged for 2.5-3.5 h. The reaction was cooled to rt and diluted with MTBE (20 mL) and water (20 mL). The aqueous (aq.) layer was cut and the organics were washed with sat'd. brine (10 mL). Upon drying over Na_2SO_4, the solvent was removed to yield crude yellow oil **8**.

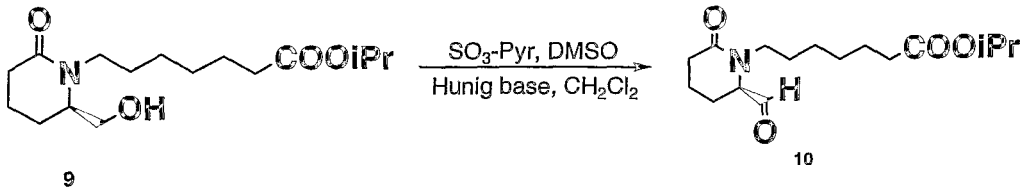
Preparative Example 9



8 **9**

To a solution of the tert-butyldimethylsilyl (TBS)-protected lactam (10g, 24.2 mmol, 1 equiv) in dry MTBE (40 mL) at 0 °C under N_2 atmosphere was added a 70% solution of HF•Pyridine (4.84g, 169 mmol, 7 equiv) over 15 min. The resulting mixture was allowed to warm to RT and aged for 12h, at which the reaction was judged complete by HPLC and ^{1}HNMR analysis. The mixture was then diluted with MTBE (100 mL) and washed with cold H_2O (30 mL). The organic layer was then treated with saturated Na_2CO_3 (25 mL), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude oil (**9**) is used directly in the next step. If desired, the alcohol can be purified by SiO_2 gel flash column chromatography (40:1 CH_2Cl_2:MeOH).

Preparative Example 10



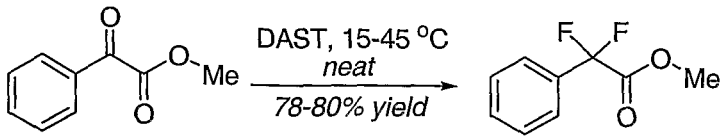
9 10

To a cold solution (0 °C) of alcohol 9 (9.46 g, 31.6 mmol), DMSO (237.3 mmol, 16.9 mL, 7.5 equiv), and Hunig base (16.5 mL, 94.9 mmol, 3 equiv) in dichloromethane (95 mL) was added SO_3•Pyridine (15 g, 94.9 mmol, 3 equiv) as a solid over 15 minutes. The resulting solution was aged at 0 °C for 1.5 h, at which complete consumption of the starting material was observed. The reaction mixture was then diluted with EtOAc (150 mL) and washed with cold 4N aqueous HCl (35 mL). The organic layer was separated and treated successively with saturated $NaHCO_3$ solution and brine. The solution then dried over $MgSO_4$ filtered and concentrated in vacuo to give the corresponding aldehyde (7.8g, 83% assay yield), which was used in the next step without further purification.

Preparative Example 11

Preparation of Sodium Phosphonate **14**

Step 1

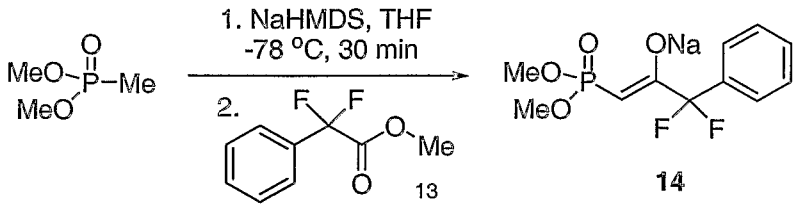


13

To a neat solution of methyl benzoylformate ($PhCOCO_2Me$, 25 g, 0.15 mol, 1 equiv) at 15 °C under N_2 atmosphere was added neat diethylaminosulfur trifluoride (DAST, 34.4 g, 0.21 mol, 1.4 equiv) at a rate such that the internal temperature was maintained below 45 °C. At the end of the addition, the resulting brown solution was allowed to cool to RT and aged for 3 more hours, at which time a complete consumption of starting material was observed by high performance liquid chromatography (HPLC) and gas chromatography/mass spectroscopy (GC/MS). The reaction mixture was then poured *slowly* into a mixture of ice/H_2O (NOTE: *exothermic!)* and the product was extracted with MTBE (3x). The combined organic layer was then neutralized slowly to a pH of 7 with a cold solution of 20% aqueous Na_2CO_3 (NOTE: *gas evolution*), washed with

brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by vacuum distillation (bp= 103-105 °C at 24-25 torr) to give the desired product (**13**) as slightly yellow oil.

Step 2

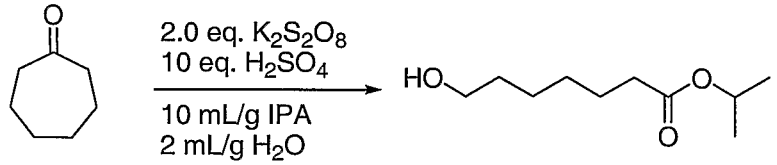


To a solution of dimethyl methylphosphonate (28g, 0.23 mol, 1.05 equiv) in dry THF (400 mL, KF= 30 ppm) under N_2 atm at -78 °C was slowly added a 2M solution of sodium bis(trimethylsilyl)amide in THF (115 mL, 0.23 mol, 1.05 equiv) over 15 min. The resulting solution was aged for 30 min and then treated with neat methyl difluoroester ($PhCF_2CO_2Me$, 40g, 0.22 mol, 1.0 equiv) over 15 min. The reaction mixture was aged at -78 °C for 1h, slowly warmed to RT and concentrated to about a quarter of its original volume and added MTBE (400mL) over 0.5h. The resulting suspension was further aged at RT for 0.5h and filtered. The wet cake was washed with MTBE (100mL) and dried *in vacuo* under a stream of N_2. The product was isolated as white solid (**14**).

Preparative Example 12

Preparation of Compound **16**

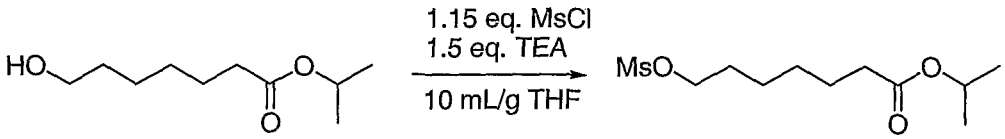
Step 1



To a 10° C solution of water (250 mL), IPA (1250 mL) and concentrated sulfuric acid (600 mL, 11.1 moles) was added solid potassium persulfate (600 g, 2.22 moles) in one portion. Cycloheptanone (131.5 mL) was diluted to 250 mL total volume with IPA and this solution was added via addition funnel to the persulfate slurry over 15 min with the temperature maintained

<15° C throughout the addition. The reaction was aged at 15° C for 16-20h. Once all of the cycloheptanone had reacted, the reaction was filtered to remove the salts, keeping the filtrate cold. The filtrate was diluted with MTBE (1250 mL), sat'd brine (1 L), and water (500mL), with the temperature maintained <30° C. Upon transfer to a separatory funnel, the phases were allowed 1h to settle and the aqueous layer was cut. The organic layer was washed with sat'd. Na_2CO_3 (2 x 1L), or until the aq. cut remained basic. The solution was diluted with hexanes (1.25 L) and dried over Na_2SO_4 for 1 h. The solvent was removed under vacuum and the oil was vacuum distilled to yield pure ester (**16**). (bp 125 ° @ 4 mm Hg)

Step 2

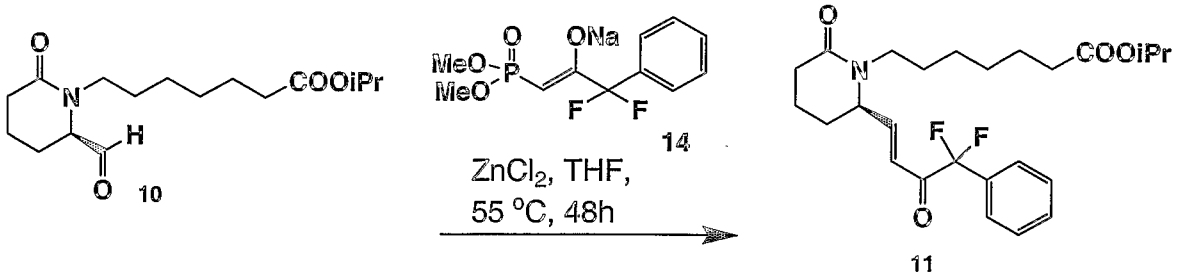


16

To a -10° C solution of ester (10 g, 0.05 moles) and triethylamine (11.1 mL, 0.08 moles) in dry THF (100 mL) was added Methanesulfonyl chloride (MsCl – 4.75 mL, 0.06 moles) (diluted 1:1 in THF) with the temperature maintained <10° C throughout the addition. The reaction was aged for 30 min @ 0-5° C. Upon completion, the reaction was diluted with hexanes (100 mL) and quenched with water (50 mL). The aq. layer was cut and the organic layer was dried over Na_2SO_4 for 30 min. The solvent was removed under vacuum and gave a yellow oil (**16**). The mesylate should be prepared fresh prior to lactam alkylation in order to minimize impurities.

Example 1

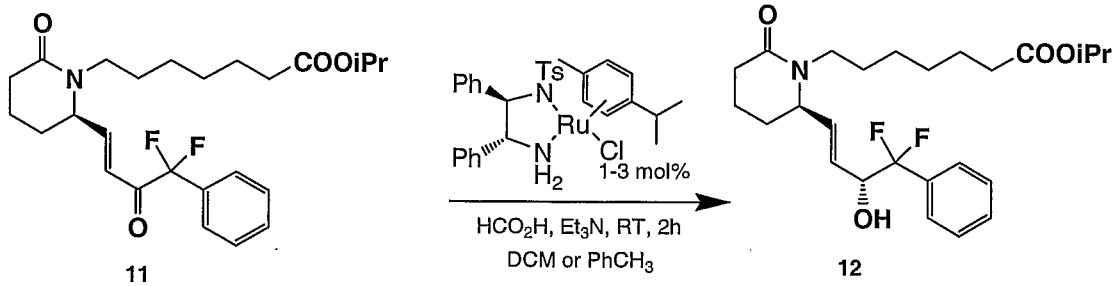
isopropyl 7-{(2*R*)-2-[(1*E*)-4,4-difluoro-3-oxo-4-phenylbut-1-en-1-yl]-6-oxopiperidin-1-yl}heptanoate



To a solution of sodium phosphonate **14** (13.7 g, 45.7 mmol, 1.4 equiv) in THF (130 mL) at 0 °C under nitrogen was added $ZnCl_2$ (3.33g, 24.5 mmol, 0.75 equiv). The resulting mixture was stirred at rt for 15 minutes and then treated with a solution of aldehyde **10** (9.7g, 32.66 mmol, 1 equiv) in THF (10 mL). The resulting suspension was then heated to 50 °C for 50h, at which a 94-97% conversion was observed. The mixture was then concentrated to about a third of its volume, diluted with EtOAc (130 mL), washed with H_2O (30 mL) and brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated to give yellow oil (**11**), which can be purified by SiO_2 gel flash chromatography (19:1 → 9:1 toluene:acetone).

Example 2

7-{(2R)-2-[(1E,3R)-4,4-difluoro-3-hydroxy-4-phenylbut-1-en-1yl]-6-oxopiperidin-1-yl}heptanoate (12)



To a solution of the enone (450 mg, 1 mmol, 1.0 equiv) in 0.5 M/~4.5mL/g anhydrous $PhCH_3$ or dichloromethane (DCM) under N_2 atmosphere was added Et_3N (0.14 mL, 1 mmol, 1.0 equiv) and HCO_2H (0.05 mL, 1.2 mmol, 1.2 equiv) at room temperature (RT). The resulting solution was stirred for 10 min and then treated with solid (R,R)-(-)-Ru-TsDPEN-cymene complex[1] (19 mg,

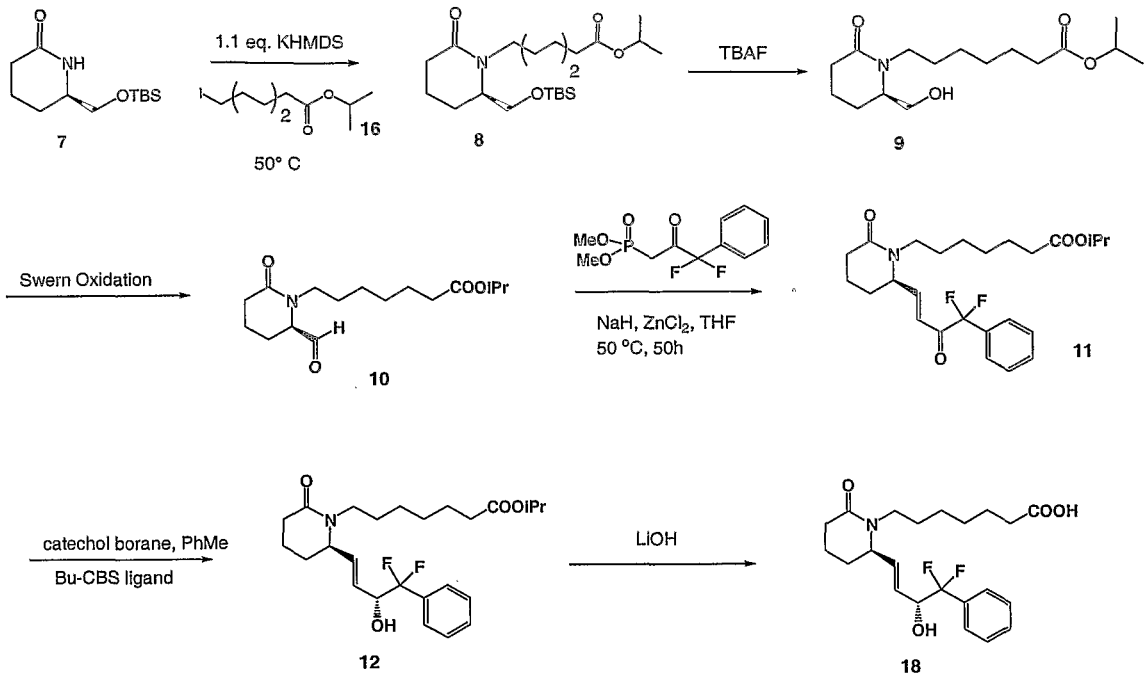
0.03 mmol, 0.03 equiv) all at once. The reaction mixture was then aged at RT for 2h, at which a complete consumption of starting material was observed. Tert-butyl methyl ether - MTBE (5 mL) was added followed by 1N HCl (2mL). The organic layer was separated, washed with saturated Na_2CO_3, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the final compound as viscous oil. (40-60:1 diastereomeric ratio, 83-85% assay yield).

The catalyst can also be generated in situ by mixing 0.02 mol equiv of $[RuCl_2(p\text{-cymene})_2]$ and 0.04 mol equiv of the (*R,R*)-*N*-Tosyl-1,2-diphenylethylene-1,2-diamine in DCM (dichloromethane) in the presence of 0.04 mol equiv of 1M solution KOtBu in THF(tetrahydrofuran). After aging for 10 min at RT, Et_3N was added followed by HCO_2H and a solution of the enone in DCM).

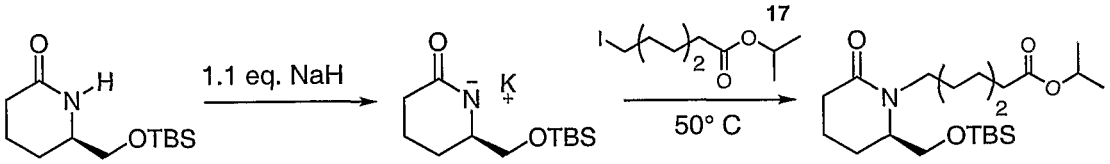
The catalyst was prepared by mixing 1mol equiv of $[RuCl_2(p\text{-cymene})_2]$, 2mol equiv (*R,R*)-*N*-Tosyl-1,2-diphenylethylene-1,2-diamine and 4.2 mol equiv of Et_3N in iPrOH at 80 °C for 1h(hour). After solvent removal, the solid was washed with cold H_2O and the recrystallized from MeOH to give the catalyst as orange solid. (65-75% yield).

Example 3: 7-{(2*R*)-2-[(1*E*, 3R)-4,4-difluoro-3-hydroxy-4-phenylbut-1-en-1-yl]-6-oxopiperidin-1-yl}heptanoic acid

Scheme 1



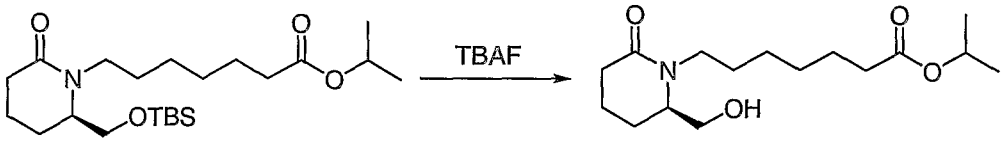
Step 1: isopropyl 7-[(2*R*)-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-6-oxopiperidin-1-yl]heptanoate



To a solution of **7** (1.0 g, 4.1 mmol, syn thesized in seven steps according to the literature procedure **Synthesis 1998**, 1141-1144.) in 12 mL DMF(dimethyl formamide) was added 60% sodium hydride (172 mg, 4.3 mmol) and the resulting solution was stirred for 30 min at 50 °C whereupon isopropyl-7-iodoheptanoate,**17**, (1.9 g, 1.6 mL, 8.2 mmol) and tetrabutylammonium iodide (50 mg) were added. The solution was stirred at 50 °C overnight after which it was cooled to room temperature, slowly poured into saturated aqueous ammonium chloride solution and was extracted with ether. The organic phases were then combined and sequentially washed with H_2O,

brine and dried over Na_2SO_4, filtered and concentrated in vacuo. The compound was purified by flash chromatography using 75-100% ethyl acetate/hexanes to yield 9 as a colorless oil. 1H NMR (500 MHz, Acetone-d6): δ 4.95 (m, 1H), 3.75 (m, 3H), 3.50 (m, 1H), 2.97 (m, 1H), 2.25 (2t, 4H), 2.00 (m, 1H), 1.93 (m, 1H), 1.82 (m, 1H), 1.70-1.56 (m, 4H), 1.52 (m, 1H), 1.40-1.28 (m, 4H), 1.22 (2s, 6H), 0.93 (s, 9H), 0.11 (s, 6H).

Step 2: isopropyl 7-[(2*R*)-2-(hydroxymethyl)-6-oxopiperidin-1-yl]heptanoate

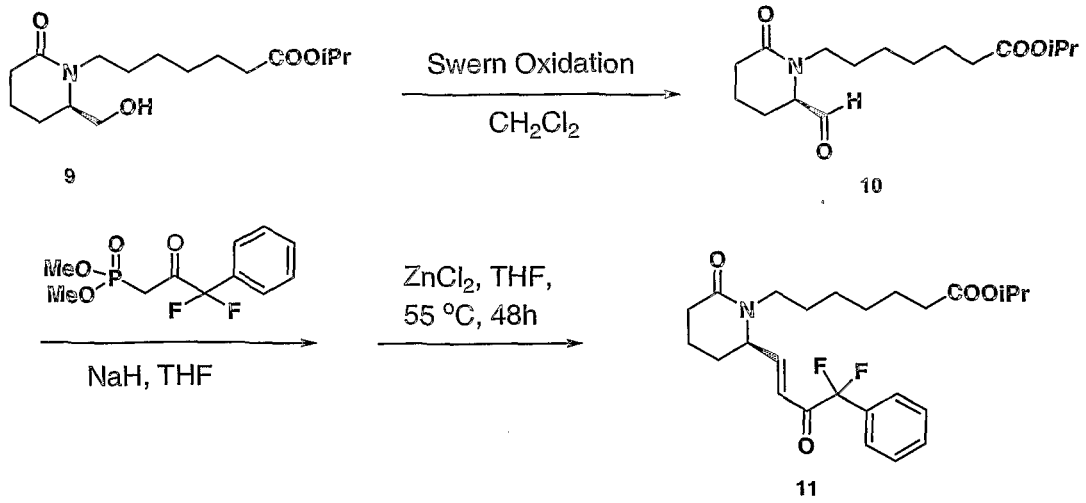


8 9

To a solution of **8** (0.80 g, 2.3 mmol) in 10 mL was added TBAF-tetrabutylammonium fluoride (0.25 mL of a 1M solution in THF) at room temperature and stirred for 18 hours. The solution was then quenched with saturated (sat'd.) $NaHCO_3$, and extracted with ethyl acetate. The organic layers were combined and washed with water then brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield **9** as a colorless oil. 1H NMR (500 MHz, Acetone-d6): δ 4.95 (m, 6H), 3.97 (t, 1H, OH), 3.76 (m, 1H), 3.66 (m, 2H), 3.48 (m, 1H), 2.98 (m, 1H), 2.24 (m, 4H), 2.08 (m, 1H), 1.90 (m, 1H), 1.79 (m, 1H), 1.70-1.56 (m, 4H), 1.50 (m, 1H), 1.40-1.27 (m, 4H), 1.22 (2s, 6H).

Step 3: isopropyl 7-{(2*R*)-2-[(1*E*)-4,4-difluoro-3-oxo-4-phenylbut-1-en-1-yl]-6-

oxopiperidin-1-yl}heptanoate

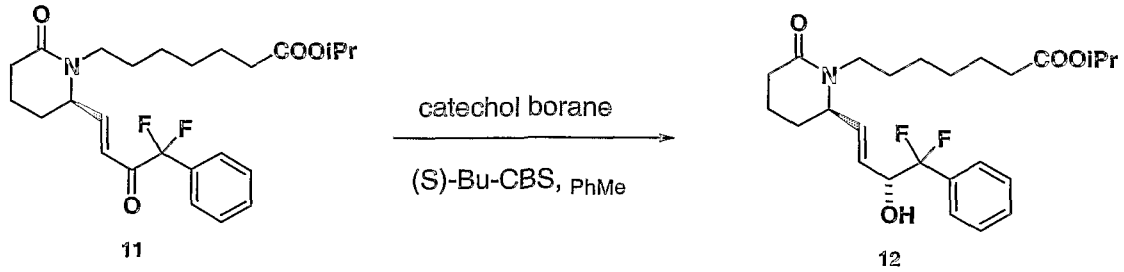


9 10 11

To a purged flask with N_2 (g) was added CH_2Cl_2 (40 mL) to which dimethylsulfoxide (0.115 g, 0.10 mL, 1.48 mmol) was then added. The solution was then cooled to –78 °C and during vigorous stirring oxalyl chloride (0.17 g, 0.12 mL, 1.3 mmol) was added dropwise. After 30 min a solution of **9** (0.35 g, 1.2 mmol) in 5 mL CH_2Cl_2 was added via cannula. Stirring was continued for another 30 min at *–78 °C. Triethyl amine (0.31 g, 0.43 mL, 3.1 mmol) was added dropwise* and after 15 min of stirring was concentrated in vacuo without the use of the bath. A solution of 1:1 diethyl ether/ethyl acetate (100 mL) was used to filter off the triethylamine salts and the solution was concentrated in vacuo. The crude aldehyde, **10**, was then diluted in 5 mL of THF and added to a solution of (2-oxo-3-phenyl-propyl)-phosphonic acid dimethyl ester (0.34 g, 1.4 mmol) and 60% sodium hydride (52 mg, 1.3 mmol) in 15 mL of THF at 0 °C which had been premixed 1 hour. Zinc chloride (x mL of a 1M solution in THF was added) and the reaction *mixture was stirred overnight at 50°C. The solution was quenched with saturated aqueous* ammonium chloride solution and was extracted with ethyl acetate. The organic phases were then combined, and sequentially washed with H_2O, brine and dried over Na_2SO_4, filtered and concentrated in vacuo. The compound was purified by flash chromatography using 50-80% ethyl acetate/hexanes to yield **11** as a colorless oil. 1H NMR (400 MHz, Acetone-d6): δ 7.65-7.55 (m, 5H), 7.11 (dd, 1H), 6.67 (d, 1H), 4.95 (m, 1H), 4.40 (m, 1H), 3.78 (m, 1H), 2.60 (m, 1H), 2.25 (m, 4H), 2.02 (m, 1H), 1.90 (m, 1H), 1.68 (m, 2H), 1.53-1.36 (m, 4H), 1.35-1.17 (m, 10H).

Step 4: isopropyl 7-{(2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-en-1-yl]-6-

oxopiperidin-1-yl}heptanoate



11 12

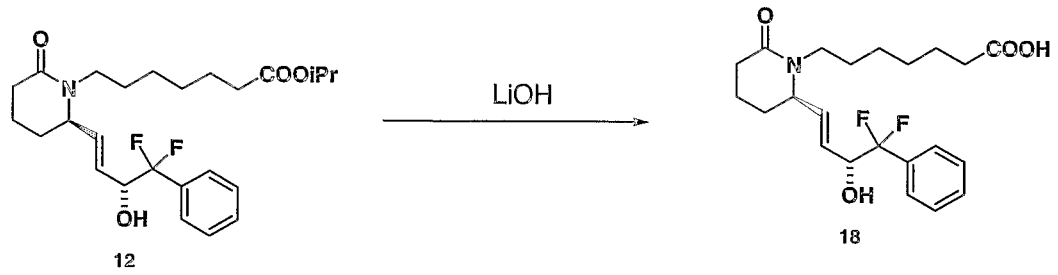
A. Synthesis of butyl-(S)-CBS in toluene: To a solution of (S)-CBS ligand (11.53 g, 45.5 mmol) in toluene (110 mL) was added butylboronic acid (5.1 g, 47.8 mmol) and the mixture was heated to reflux over night with a Dean stark. This final solution was 0.48 M and was used directly.

B. Reduction: To a solution of catecholborane (3.35 mL, 31.4 mmol) in toluene (400 mL) cooled to -78 °C was added 68 mL (32.6 mmol) of (S)-2-butyl-CBS oxazaborolidine solution under nitrogen and the mixture was stirred at the temperature for 1 hour (h). Ketone **11** (7 g, 15.6 mmol) in toluene (420 mL) was added dropwise in 1 h under nitrogen and the mixture stirred at the temperature until all starting material disappeared (usually in 30 min). To the mixture was then added 200 mL 1N HCl and the mixture allowed to warm to room temperature with vigorous stirring. The mixture was extracted with ethyl acetate (emulsion developed during extraction and the suspension was filtered through celite to remove emulsion). The crude product was purified by flash chromatograph. Eluting with EA/hexanes (70-100%) gave the desired alcohol as a mixture of two diastereomers in a ratio of 12:1. The mixture was easily separated by prep HPLC (high performance liquid chromatograpy) using a chiral Pak AD® column using 50% iPrOH in hexanes as eluants (monitoring at λ 214 nm). The undesired isomer came out first followed by the desired isomer **12**.

^{1}H NMR (400 MHz, Acetone-d_6): δ 7.6-7.5 (m, 2H), 7.5-7.4 (m, 3H), 5.80 (dd, 1H), 5.6 (dd, 1H), 5.0-4.9 (m, 2H), 4.7-4.6 (m, 1H), 4.1-4.0 (m, 1H), 3.8-3.7 (m, 1H), 2.6-2.5 (m,1H), 2.3-2.2 (m, 4H), 1.9-1.8 (m, 1H), 1.75-1.55 (m, 5H), 1.55-1.4(m, 2H), 1.4-1.22 (m, 4H), 1.22 (d, 6H).

Step 5: 7-{(2*R*)-2-[(1*E*, 3R)-4,4-difluoro-3-hydroxy-4-phenylbut-1-en-1-yl]-6-oxopiperidin-1-yl}

heptanoic acid



12 18

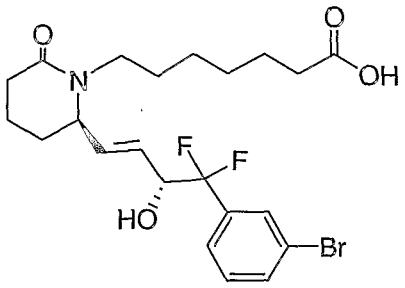
To a solution of **12** (39 mg, 0.089 mmol) in 2.75 mL 2.5:2.5:1 THF:MeOH:water, at 0 °C, was added lithium hydroxide (145 µL of a 2M solution in water) and the resulting solution was allowed to warm to room temperature and stirred overnight. To the solution was added a 1M aqueous solution of HCl (1 mL) and the solution was extracted with ethyl acetate. The organic phases were then combined, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The compound was purified by flash chromatography using 49-45%/1-5%/1 drop CH_2Cl_2/methanol/acetic acid to yield **18** as a colorless oil. 1H NMR (500 MHz, Acetone-d6): δ 7.6-7.5 (m, 5H), 5.8 (dd, 1H), 5.6 (dd, 1H), 5.6 (bs, 1H), 4.6 (m, 1H), 4.1 (m, 1H), 3.7 (m, 1H), 2.6 (m, 1H), 2.4-2.2 (m, 4H), 1.9-1.2 (m, 12H).

The following Examples 4 through 13 can be made in accordance with Examples 1-3 with the appropriate modifications.

Example 4

7-{(2*R*)-2-[(3*R*)-4-(3-bromophenyl)-4,4-difluoro-3-hydroxybutyl]-6-oxopiperidin-1-yl}heptanoic acid

MS (+ESI): M/Z 490.1 $(M+1)^+$.

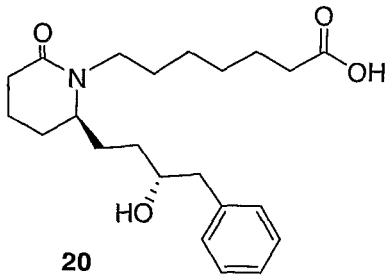


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Example 5

7-{[(2*R*)-2-(3*R*)-3-hydroxy-4-phenyl-butyl]-6-oxo-piperdin-1-yl} heptanoic acid

^{1}H NMR (400 MHZ, CD_3OD): δ 7.3-7.1 (M, 5H), 3.8-3.7 (M, 2H), 3.4 (M, 1H), 2.9-2.7(M, 3H), 2.3 (M, 4H), 1.9-1.3 (M, 16H); MS (-ESI): M/Z 374.2 $(M-1)^-$.

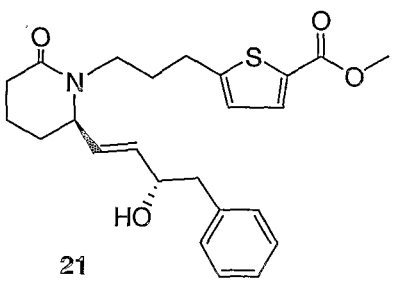


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Example 6

methyl 5-{3-[(2*R*)-2-((1*E*)-(3*S*) 3-hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-propyl}-thiophene-2-carboxylate

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.6 (d, 1H), 7.2-7.1 (m, 5H), 6.7 (d, 1H), 5.5 (m, 2H), 4.3 (m, 1H), 3.8-3.7 (m, 2H), 3.8 (s, 3H), 2.8-2.6 (m, 6H), 2.3-2.2 (m, 2H), 1.9-1.2 (m, 6H).

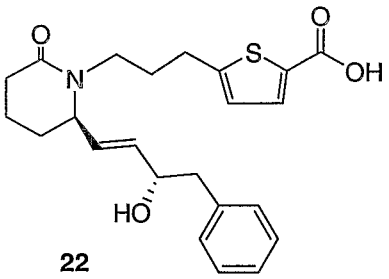


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Example 7

5-{3-[(2*R*)-2-((1*E*)-(3*S*) 3-hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-propyl}-thiophene-2-carboxylic acid

^{1}H NMR (400 MHZ, CD_3OD): δ 7.6 (D, 1H), 7.2-7.1 (M, 5H), 6.9 (D, 1H), 5.5 (M, 2H), 4.3 (M, 1H), 3.9 (M, 1H), 3.7 (M, 1H), 2.9-2.6 (M, 5H), 2.2 (M, 2H), 1.9-1.5 (M, 6H); MS (-ESI): M/Z 412.1 $(M-1)^-$.

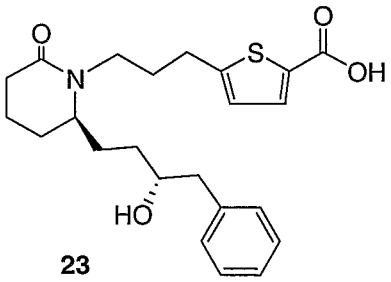


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Example 8

5-{3-[(2*R*)-2-((3*S*) 3-hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-propyl}-thiophene-2-carboxylic acid

^{1}H NMR (400 MHZ, CD_3OD): δ 7.6 (D, 1H), 7.3-7.1 (M, 5H), 6.9 (D, 1H), 3.8 (M, 2H), 3.4 (M, 1H), 3.0-2.9 (M, 1H), 2.8-2.5(M, 4H), 2.3 (M, 2H), 2.0-1.3 (M, 10H); MS (-ESI): M/Z 414.1 $(M-1)^-$.

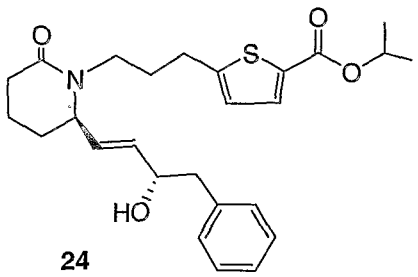


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Example 9

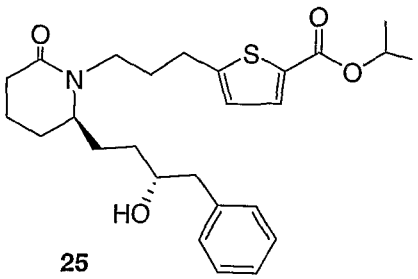
isopropyl 5-{3-[(2*R*)-2-((1*E*)-(3*S*) 3-hydroxy-4-phenyl-but-1-enyl)-6-oxo-piperidin-1-yl]-propyl}-thiophene-2-carboxylate

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.6 (d, 1H), 7.3-7.1 (m, 5H), 6.8 (d, 1H), 5.5 (m, 2H), 5.1 (m, 1H), 4.4 (m, 1H), 3.9-3.8 (m, 2H), 3.3 (br s, 1H), 2.8 (m, 4H), 2.7 (m, 1H), 2.3 (m, 2H), 1.9-1.6 (m, 6H), 1.3 (dd, 6H); MS (+ESI):
M/Z 456.4 $(M+1)^+$.



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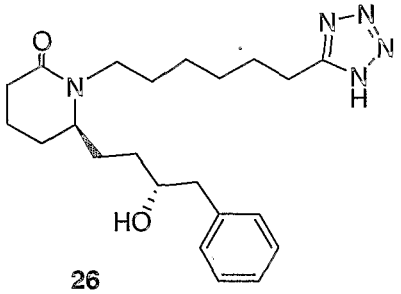
Example 10
isopropyl 5-{3-[(2*R*)-2-((3*S*) 3-hydroxy-4-phenyl-butyl)-6-oxo-piperidin-1-yl]-propyl}-thiophene-2-carboxylate
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.6 (d, 1H), 7.3-7.1 (m, 5H), 6.8 (d, 1H), 5.2 (m, 1H), 3.9-3.8 (m, 2H), 3.3 (m, 1H), 2.9-2.8 (m, 4H), 2.7-2.6 (m, 1H), 2.4-2.3 (m, 3H), 2.0-1.2 (m, 10H), 1.3 (d, 6H); MS (+ESI): M/Z 458.2 $(M+1)^+$.



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Example 11
6-[(3*R*)-3-hydroxy-4-phenyl-butyl]-1-[6-(1*H*-tetrazol-5-yl)-hexyl]-piperidin-2-one
^{1}H NMR (400 MHz, CD_3OD): δ 7.3-7.1 (m, 5H), 3.8-3.7 (m, 2H), 3.3 (m, 1H), 2.9-2.7 (m, 5H),

2.3 (m, 2H), 1.9-1.3 (m, 16H); MS (+ESI): M/Z 400.3 $(M+1)^+$.

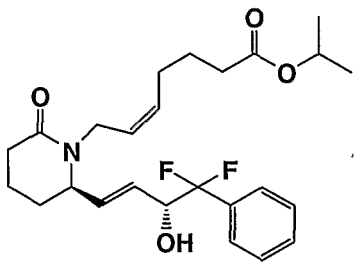


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Example 12

isopropyl (5Z)-7-{(2R)-2-[(1E,3R)-4,4-difluoro-3-hydroxy-4-phenylbut-1-en-1-yl]-6-oxopiperidin-1-yl}hept-5-enoate

MS (+ESI): M/Z 450.3 $(M+1)^+$.

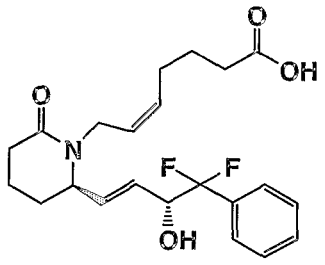


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Example 13

(5Z)-7-{(2R)-2-[(1E,3R)-4,4-difluoro-3-hydroxy-4-phenylbut-1-en-1-yl]-6-oxopiperidin-1-yl}hept-5-enoic acid.

MS (-ESI): m/z 406.1 (M-1)$^-$.



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I. Effects of an EP4 Agonist on Intraocular Pressure (IOP) in Rabbits and Monkeys.

Animals

Drug-naïve, male Dutch Belted rabbits and female cynomolgus monkeys are used in this study. Animal care and treatment in this investigation are in compliance with guidelines by the National Institute of Health (NIH) and the Association for Research in Vision and Ophthalmology (ARVO) resolution in the use of animals for research. All experimental procedures str approved by the Institutional Animal Care and Use Committee of Merck and Company.

Drug Preparation and Administration

Drug concentrations are expressed in terms of the active ingredient (base). The compounds of this invention are dissolved in physiological saline at 0.01, 0.001, 0.0001 % for rabbit study and 0.05, 0.005% for monkey studies. Drug or vehicle aliquots (25 ul) are administered topically unilaterally or bilaterally. In unilateral applications, the contralateral eyes receive an equal volume of saline. Proparacaine (0.5%) is applied to the cornea prior to tonometry to minimize discomfort. Intraocular pressure (IOP) is recorded using a pneumatic tonometer (Alcon Applanation Pneumatonograph) or equivalent.

Analysis

The results are expressed as the changes in IOP from the basal level measured just prior to administration of drug or vehicle and represent the mean, plus or minus standard deviation. Statistical comparisons are made using the Student's t-test for non-paired data between

responses of drug-treated and vehicle-treated animals and for paired data between ipsilateral and contralateral eyes at comparable time intervals. The significance of the date is also determined as the difference from the "t-0" value using Dunnett's "t" test. Asterisks represent a significance level of $p<0.05$.

A. Intraocular Pressure Measurement in Rabbits

Male Dutch Belted rabbits weighing 2.5-4.0 kg are maintained on a 12- hour light/dark cycle and rabbit chow. All experiments are performed at the same time of day to minimize variability related to diurnal rhythm. IOP is measured before treatment then the compounds of this invention or vehicle are instilled (one drop of 25 ul) into one or both eyes and IOP is measured at 30, 60, 120, 180, 240, 300, and 360 minutes after instillation. In some cases, equal number of animals treated bilaterally with vehicle only are evaluated and compared to drug treated animals as parallel controls.

B. Intraocular Pressure Measurements in Monkeys.

Unilateral ocular hypertension of the right eye is induced in female cynomolgus monkeys weighing between 2 and 3 kg by photocoagulation of the trabecular meshwork with an argon laser system (Coherent NOVUS 2000, Palo Alto, USA) using the method of Lee at al. (1985). The prolonged increase in intraocular pressure (IOP) results in changes to the optic nerve head that are similar to those found in glaucoma patients.

For IOP measurements, the monkeys are kept in a sitting position in restraint chairs for the duration of the experiment. Animals are lightly anesthetized by the intramuscular injection of ketamine hydrochloride (3-5 mg/kg) approximately five minutes before each IOP measurement and one drop of 0.5% proparacaine was instilled prior to recording IOP. IOP is measured using a pneumatic tonometer (Alcon Applanation Tonometer) or a Digilab pneumatonometer (Bio-Rad Ophthalmic Division, Cambridge, MA, USA).

IOP is measured before treatment and generally at 30, 60, 124, 180, 300, and 360 minutes after treatment. Baseline values are also obtained at these time points generally two or three days prior to treatment. Treatment consists of instilling one drop of 25 ul of the compounds of this invention (0.05 and 0.005 %) or vehicle (saline). At least one-week washout period is employed before testing on the same animal. The normotensive (contralateral to the hypertensive) eye is treated in an exactly similar manner to the hypertensive eye. IOP measurements for both eyes are compared to the corresponding baseline values at the same time

point. Results are expressed as mean plus-or-minus standard deviation in mm Hg. The activity range of the compounds of this invention for ocular use is between 0.01 and 100,000 nM.

II. Radioligand binding assays:

The assays used to test these compounds were performed essentially as described in: Abramovitz M, Adam M, Boie Y, Carriere M, Denis D, Godbout C, Lamontagne S, Rochette C, Sawyer N, Tremblay NM, Belley M, Gallant M, Dufresne C, Gareau Y, Ruel R, Juteau H, Labelle M, Ouimet N, Metters KM. The utilization of recombinant prostanoid receptors to determine the affinities and selectivities of prostaglandins and related analogs. Biochim Biophys Acta 2000 Jan 17;1483(2):285-293 and discussed below:

Stable expression of prostanoid receptors in the human embryonic kidney (HEK) 293(EBNA) cell line

Prostanoid receptor (PG) cDNAs corresponding to full length coding sequences were subcloned into the appropriate sites of the mammalian expression vector pCEP4 (Invitrogen) pCEP4PG plasmid DNA was prepared using the Qiagen plasmid preparation kit (QIAGEN) and transfected into HEK 293(EBNA) cells using LipofectAMINE@ (GIBCO-BRL) according to the manufacturers' instructions. HEK 293(EBNA) cells expressing the cDNA together with the hygromycin resistance gene were selected in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10 % heat inactivated fetal bovine serum, 1 mM sodium pyruvate, 100 U/ml Penicillin-G, 100 μg/ml Streptomycin sulphate, 250 μg/ml active GENETICIN™ (G418) (all from Life Technologies, Inc./BRL) and 200 μg/ml hygromycin (Calbiochem). Individual colonies were isolated after 2-3 weeks of growth under selection using the cloning ring method and subsequently expanded into clonal cell lines. Expression of the receptor cDNA was assessed by receptor binding assays.

HEK 293(EBNA) cells were grown in supplemented DMEM complete medium at 37°C in a humidified atmosphere of 6 % CO_2 in air, then harvested and membranes prepared by differential centrifugation (1000 x g for 10 min, then 160,000 x g for 30 min, all at 4°C) following lysis of the cells by nitrogen cavitation at 800 psi for 30 min on ice in the presence of protease inhibitors (2 mM phenylmethylsulfonylfluoride, 10 μM E-64, 100 μM leupeptin and 0.05 mg/ml pepstatin). The 160,000 x g pellets were resuspended in 10 mM HEPES/KOH (pH 7.4) containing 1 mM EDTA at approximately 5-10 mg/ml protein by Dounce homogenisation (Dounce A; 10 strokes), frozen in liquid nitrogen and stored at -80°C.

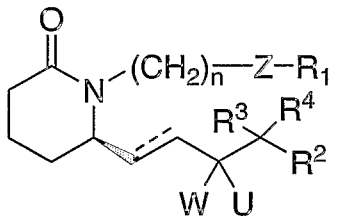
Prostanoid receptor binding assays

Prostanoid receptor binding assays were performed in a final incubation volume of 0.2 ml in 10 mM MES/KOH (pH 6.0) (EP subtypes, FP and TP) or 10 mM HEPES/KOH (pH 7.4) (DP and IP), containing 1 mM EDTA, 10 mM $MgCl_2$ (EP subtypes) or 10 mM $MnCl_2$ (DP, FP, IP and TP) and radioligand [0.5-1.0 nM [^{3}H]PGE_2 (181 Ci/mmol) for EP subtypes, 0.7 nM [^{3}H]PGD_2 (115 Ci/mmol) for DP, 0.95 nM [^{3}H]$PGF_{2\alpha}$ (170 Ci/mmol) for FP, 5 nM [^{3}H]iloprost (16 Ci/mmol) for IP and 1.8 nM [^{3}H]SQ 29548 (46 Ci/mmol) for TP]. EP_3 assays also contained 100 μM GTPγS. The reaction was initiated by addition of membrane protein (approximately 30 μg for EP_1, 20 μg for EP_2, 2 μg for EP_3, 10 μg for EP_4, 60 μg for FP, 30 μg for DP, 10 μg for IP and 10 μg for TP) from the 160,000 x g fraction. Ligands were added in dimethylsulfoxide (Me_2SO) which was kept constant at 1 % (v/v) in all incubations. Non-specific binding was determined in the presence of 1 μM of the corresponding non-radioactive prostanoid. Incubations were conducted for 60 min (EP subtypes, FP and IP) or 30 min (DP and TP) at 30°C (EP subtypes, DP, FP and TP) or room temperature (IP) and terminated by rapid filtration through a 96-well Unifilter GF/C (Canberra Packard) prewetted in assay incubation buffer without EDTA (at 4°C) and using a Tomtec Mach III 96-well semi-automated cell harvester. The filters were washed with 3-4 ml of the same buffer, dried for 90 min at 55°C and the residual radioactivity bound to the individual filters determined by scintillation counting with addition of 50 μl of Ultima Gold F (Canberra Packard) using a 1450 MicroBeta (Wallac). Specific binding was calculated by subtracting non-specific binding from total binding. Specific binding represented 90-95 % of the total binding and was linear with respect to the concentrations of radioligand and protein used. Total binding represented 5-10 % of the radioligand added to the incubation media.

The activity range of the compounds of this invention for bone use is between 0.01 and 100,000 nM.

WHAT IS CLAIMED IS:

1. A compound having the structural formula I:



FORMULA I

or a pharmaceutically acceptable salt, enantiomer, diastereomer, prodrug or mixture thereof, wherein,

U represents H, C1-3 alkyl or is not present when W is =O;

W represents OH or =O, provided that U is not present when W is =O;

Z represents $(CH_2)_n$ or CH=CH;

R^1 represents $(CH_2)_p$hydroxy, ($(CH_2)_pCO_2R^{10}$, or $(CH_2)_n$heterocyclyl, said heterocyclyl unsubstituted or substituted with 1 to 3 groups of R^a and optionally containing an acidic hydroxyl group;

R^2 independently represents C_{1-10} alkyl, $(CH_2)_mC_{6-10}$aryl, $(CH_2)_mC_{5-10}$heterocyclyl, $(CH_2)_mC_{3-10}$ heterocycloalkyl, $(CH_2)_mC_{3-8}$ cycloalkyl, said alkyl, cycloalkyl, heterocycloalkyl, aryl or heterocyclyl unsubstituted or substituted with 1-3 groups of R^a;

R^3 and R^4 independently represent hydrogen, halogen, or C_{1-6} alkyl;

R^6 represents hydrogen, or C_{1-4} alkyl;

R^{10} represents hydrogen, C_{1-10} alkyl, C_{3-10} cyclcoalkyl, $(CH_2)pC_{6-10}$ aryl, $(CH_2)pC_{5-10}$ heterocyclyl;

R^a represents C_{1-6} alkoxy, C_{1-6} alkyl, CF_3, nitro, amino, cyano, C_{1-6} alkylamino, halogen, or Ra further represents for aryls and heterocyclyl, SC_{1-6}alkyl, SC_{6-10}aryl, SC_{5-10}heterocyclyl, OC_{6-10}aryl, OC_{5-10}heterocyclyl, CO_2R^6, CH_2OC_{1-6} alkyl, CH_2SC_{1-6} alkyl, CH_2Oaryl, CH_2Saryl;

--- represents a double or single bond;
p represents 0-3;
n represents 0-4; and
m represents 0-8.

2. A compound in accordance with claim 1 wherein R^1 is $(CH_2)_pCO_2R^{10}$, R^3 and R^4 are halogen, and R^2 is $(CH_2)_mC_{6-10}$aryl, said aryl unsubstituted or substituted with 1 to 3 groups of R^a.

3. A compound which is:
7-{(2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-6-oxopiperidin-1-yl}heptanoic acid;
isopropyl 7-{(2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-6-oxopiperidin-1-yl}heptanoate;
isopropyl (5Z)-7-{(2R)-2-[(1E,3R)-4,4-difluoro-3-hydroxy-4-phenylbut-1-en-1-yl]-6-oxopiperidin-1-yl}hept-5-enoate;
(5Z)-7-{(2R)-2-[(1E,3R)-4,4-difluoro-3-hydroxy-4-phenylbut-1-en-1-yl]-6-oxopiperidin-1-yl}hept-5-enoic acid;
7-{[(2*R*)-2-(3*R*)-3-hydroxy-4-phenyl-butyl]-6-oxo-piperdin-1-yl} heptanoic acid;
isopropyl 7-{(2*R*)-2-[(1*E*)-4,4-difluoro-3-oxo-4-phenylbut-1-enyl]-6-oxopiperidin-1-yl}heptanoate;
6-[(3*R*)-3-hydroxy-4-phenyl-butyl]-1-[6-(1*H*-tetrazol-5-yl)-hexyl]-piperidin-2-one;
(6*S*)-6-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-1-[6-(2*H*-tetraazol-5-yl)hexyl]piperazin-2-one;
(6*R*)-6-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-1-[6-(2*H*-tetraazol-5-yl)hexyl]piperidin-2-one;

7-{(2*R*)-2-[(3*R*)-4-(3-bromophenyl)-4,4-difluoro-3-hydroxybutyl]-6-oxopiperidin-1-yl}heptanoic acid;

or a pharmaceutically acceptable salt, enantiomer, diastereomer, prodrug or mixture thereof.

4. A method for treating ocular hypertension or glaucoma comprising administration to a patient in need of such treatment a therapeutically effective amount of a compound of claim 1.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula I, as recited in claim 1, 2 or 3, said composition administered in a topical formulation as a solution or suspension.

6. The composition according to claim 4 wherein one or more active ingredients belonging to the group consisting of: β-adrenergic blocking agent, parasympathomimetic agent, sympathomimetic agent, carbonic anhydrase inhibitor, Maxi-K channel blocker, and a prostaglandin, hypotensive lipid, neuroprotectant, and 5-HT2 receptor agonist is added to the topical formulation.

7. The composition according to claim 6 wherein the β-adrenergic blocking agent is timolol, betaxolol, levobetaxolol, carteolol, or levobunolol; the parasympathomimetic agent is pilocarpine; the sympathomimetic agent is epinephrine, brimonidine, iopidine, clonidine, or para-aminoclonidine, the carbonic anhydrase inhibitor is dorzolamide, acetazolamide, metazolamide or brinzolamide; COSOPT®, the Maxi-K is Penitrem A, paspalicine, charybdotoxin, iberiotoxin, Paxicillan, Aflitram, Verroculogen, 1-(1-isobutyl-6-methoxy-1H-indazol-3-yl)-2-methylpropan-1-one; 1-[1-(2,2-dimethylpropyl)-6-methoxy-1H-indazol-3-yl]-2-methylpropan-1-one; 1-[1-(cyclohexylmethyl)-6-methoxy-1H-indazol-3-yl]-2-methylpropan-1-one; 1-(1-hexyl-6-methoxy-1H-indazol-3-yl)-2-methylpropan-1-one; 1-[1-(2-ethylhexyl)-6-methoxy-1H-indazol-3-yl]-2-methylpropan-1-one; 1-(3-isobutyryl-6-methoxy-1H-indazol-1-yl)buan-2-one; 1-(3-isobutyryl-6-methoxy-1H-indazol-1-yl)-3,3-dimethylbutan-2-one; 1-(3-cyclopentylcarbonyl)-6-methoxy-1H-indazol-1-yl)-3,3-dimethylbutan-2-one; 1-(3,3-dimethyl-2-oxobutyl) -6-methoxy-1H-indazole-3-carboxylic acid; and 1-[3-(3-hydroxypropanoyl) -6-methoxy-1H-indazol-1-yl]-3,3-dimethylbutan-2-one, the prostaglandin is latanoprost, travaprost, unoprostone, rescula, or S1033, the hypotensive lipid is lumigan, the neuroprotectant is eliprodil, R-eliprodil or memantine; and the 5-HT2 receptor agonist is 1-(2-aminopropyl)-3-methyl-1H-imdazol-6-ol fumarate or 2-(3-chloro-6-methoxy-indazol-1-yl)-1-methyl-ethylamine.

8. A method for treating macular edema or macular degeneration, treating dry eye, increasing retinal and optic nerve head blood velocity, increasing retinal and optic nerve oxygen tension or providing a neuroprotection, comprising administration to a patient in need of such treatment a pharmaceutically effective amount of a compound of a compound as recited in claim 1.

9. The method according to Claim 4 wherein the compound of formula I is applied as a topical formulation and an active ingredient belonging to the group consisting of β-adrenergic blocking agent, parasympatho-mimetic agent, sympathomimetic agent, carbonic anhydrase inhibitor, COSOPT®, Maxi-K channel blocker and a prostaglandin, hypotensive lipid, neuroprotectant, and 5-HT2 receptor agonist is added to the formulation.

10. A method according to claim 6 in which the topical formulation optionally contains xanthan gum or gellan gum.

11. Use of a compound of formula I, as defined in claim 1, 2 or 3, or a pharmaceutically acceptable salt, enantiomer, diastereomer, prodrug or mixture thereof, in the manufacture of a medicament for treating ocular hypertension or glaucoma.

12. A compound of formula I, as defined in claim 1, 2 or 3, or a pharmaceutically acceptable salt, enantiomer, diastereomer, prodrug or mixture thereof, for use in a medicinal therapy.

13. Use of a compound of formula I, as defined in claim 1, 2 or 3, or a pharmaceutically acceptable salt, enantiomer, diastereomer, prodrug or mixture thereof, in the manufacture of a medicament for treating macular edema or macular degeneration, dry eye, increasing retinal and optic nerve head blood velocity, increasing retinal and optic nerve oxygen tension or providing neuroprotection.