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Demandeur/Applicant: AERIE PHARMACEUTICALS, INC., US
Inventeurs/Inventors: DELONG, MITCHELL, A., US;
STURDIVANT, JILL, MARIE, US
Agent: LEDGLEY LAW

Titre : SELS D'ACIDES AMINES DE PROSTAGLANDINES
Title: AMINO ACID SALTS OF PROSTAGLANDINS

FIG. 1

Abstract:
The present invention is directed to novel amino acid prostaglandin salts and methods of making and using them.
(54) Title: AMINO ACID SALTS OF PROSTAGLANDINS

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AMINO ACID SALTS OF PROSTAGLANDINS

CROSS-REFERENCE TO RELATED APPLICATIONS


TECHNICAL FIELD

The present invention is directed to novel amino acid salts of prostaglandins and methods of making and using the same.

BACKGROUND OF THE INVENTION


All naturally occurring prostaglandins, including PGF2α, and almost all non-naturally-occurring prostaglandins possess a carboxylic acid moiety at the C1 position. The carboxylic acid moiety is a site for metabolic degradation by beta oxidation, which contributes to the rapid metabolism of the naturally occurring prostaglandins. Attempts to prevent beta oxidation by modifying the carboxylic acid moiety at the 1 position as an ester moiety, a sulfonamide moiety, and as a tetrazole are known in the art (See e.g. PCT Publication No. WO 99/12895, 1999; PCT Publication No. WO 99/12896, 1999; PCT
Publication No. WO 99/12898). However, such modifications have either resulted in only modest increases in half-life (such as the esters) or resulted in compounds with diminished potency.

Prostaglandin F analogs wherein C₁ itself is replaced with a heteroatom have also been described in the art. For example, PGF analogs containing a sulfonic acid moiety at C₁ (The chemistry of prostaglandins containing the sulfo group. Iguchi, Y.; Kori, S.; Hayashi, M. J. Org. Chem., 40, pp. 521-523 1975) and PGF analogs containing a phosphonic acid moiety at C₁ (The Synthesis of dimethylphosphonoprostaglandin analogs, Kluender, H. C. & Woessner, W. Prostaglandins and Medicine, 2; pp.441-444, 1979) have been disclosed. However, such compounds suffer from significantly diminished potency. However, the potent C₁ carboxylic acids are difficult to purify as they are most often synthesized as oils. There is a need for solid forms of prostaglandins, both naturally and non-naturally occurring, for the purposes of purification and as intermediates in synthesis, as well as the direct use of these solids in drug products.

SUMMARY OF THE INVENTION

The present invention provides an amino acid salt of a prostaglandin free acid.

Further, the present invention provides an amino acid prostaglandin free acid salt, wherein the amino acid is selected from the group consisting of arginine, homoarginine, N(delta)-methyl-L-arginine, L-canavanine, D-canavanine, DL-canavanine, L-α-amino-β-guanidinopropionic acid, γ-guanidinobutyric acid, and citrulene; and wherein the prostaglandin free acid is selected from the group consisting of latanoprost free acid, travoprost free acid, fluprostanol free acid, tafluprost free acid, and bitamoprost free acid.

In another embodiment, the present invention provides a pharmaceutical composition including the salt of a prostaglandin free acid and a pharmaceutically acceptable carrier. The present invention also provides methods of making the salt comprising reacting an amino acid with a prostaglandin free acid.

The invention further provides methods of making a prostaglandin analog from the salt of a prostaglandin free acid. In addition, the invention provides methods of making prostaglandins from the salts.

The present invention also provides methods of treating eye diseases, such as glaucoma, treating bone disorders, such as osteoporosis, treating skin disorders, treating respiratory disorders, treating circulatory disorders such as hypertension, treating gastrointestinal disorders, treating hair loss, fertility control, improving nasal patency or treating neurogenic bladder comprising administering an amino acid salt of a prostaglandin free acid. In addition, the present invention provides method of reducing ocular pressure comprising contacting a cell with an amount of the salt effective to reduce ocular pressure.
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an image of recrystallized Latanoprost-L-Arginine salt 2, described in Example 88, at 400x magnification.

Figure 2 is an image of recrystallized Latanoprost-L-Arginine salt 2, described in Example 88, at 400x magnification.

Figure 3 is an image of recrystallized Latanoprost-L-Arginine salt 2, described in Example 88, at 400x magnification.

Figure 4 is an image of recrystallized Latanoprost-L-Arginine salt 2, described in Example 88, at 40x magnification.

Figure 5 is an image of recrystallized Latanoprost-L-Arginine salt 2, described in Example 88, at 40x magnification.

Figure 6 is an image of recrystallized Latanoprost-L-Arginine salt 2, described in Example 88, at 40x magnification.

Figure 7 is an image of recrystallized Latanoprost-L-Arginine salt 2, described in Example 88, at 400x magnification.

Figure 8 is an image of recrystallized Latanoprost-L-Arginine salt 2, described in Example 88, at 400x magnification.

Figure 9 is an image of recrystallized Latanoprost-L-Arginine salt 2, described in Example 88, at 400x magnification.

Figure 10 is an image of recrystallized Latanoprost-L-Arginine salt 2, described in Example 88, at 400x magnification.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to novel amino acid salts of prostaglandin free acids and methods of making and using the amino acid prostaglandin salts of the present invention. The amino acid prostaglandin salts are useful in methods of treating eye diseases, such as glaucoma. The amino acid prostaglandin salts of the present invention are also useful in a method of treating bone disorders, such as osteoporosis, treating skin disorders, treating respiratory disorders, treating circulatory disorders such as hypertension, treating gastrointestinal disorders, treating hair loss, fertility control, improving nasal patency or treating neurogenic bladder. Further, the amino acid prostaglandin salts of the present invention are useful for purifying prostaglandins and prostaglandin intermediates and as intermediates in the production of both protected and unprotected prostaglandin analogs.

Definitions and Usage of Terms
“Alcohol protecting group” refers to a protecting group that replaces the active hydrogen of a hydroxyl moiety thus preventing undesired side reaction at the hydroxyl moiety. Use of alcohol protecting groups in organic synthesis is well known in the art. Examples of alcohol protecting groups are found in Chapter 2 of Theodora W. Greene’s text entitled: “Protective Groups in Organic Synthesis” (3rd Edition). Suitable alcohol protecting groups include silyl ethers, alkoxyalkyl ethers, tetrahydropyranyl, tetrahydrofuranyl, esters, and substituted or unsubstituted benzyl ethers. If more than one alcohol protecting group is present, the alcohol protecting groups may be the same or different. In some embodiments, the alcohol protecting groups may be orthogonal.

“Alkyl” refers to a saturated or unsaturated hydrocarbon chain having 1 to 18 carbon atoms, suitably 1 to 12 carbon atoms, or 1 to 6 carbon atoms, or 1 to 4 carbon atoms. Alkyl groups may be straight or branched. In some embodiments, branched alkyl groups have one or two branches. Unsaturated alkyl groups have one or more double bonds and/or one or more triple bonds. Suitably, unsaturated alkyl groups have one or two double bonds or one triple bond. Alkyl chains may be unsubstituted or substituted with from 1 to about 4 substituents unless otherwise specified. Suitably, alkyl groups are mono-, di-, or tri-substituted. Suitable alkyl substituents include, but are not limited to, cyano, halo, hydroxy, aryl (e.g., phenyl, tolyl, alkylphenyl, alkylxycarbonylphenyl, halophenyl), heterocyclyl, and heteroaryl.

“Aromatic ring” refers to an aromatic hydrocarbon ring system. Aromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic aromatic rings contain from about 5 to about 10 carbon atoms, suitably from 5 to 7 carbon atoms, or from 5 to 6 carbon atoms in the ring. Bicyclic aromatic rings contain from 8 to 12 carbon atoms, suitably 9 or 10 carbon atoms in the ring. Aromatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Suitable aromatic ring substituents include, but are not limited to, halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. Suitably, the aromatic ring substituents are lower alkyl, cyano, halo or halo alkyl.

“Basic amino acid” refers to naturally-occurring and non-naturally-occurring alpha, beta and gamma amino acids, including all enantiomers and diastereomers, whether protected or unprotected, provided that the amino acids have a net positive charge at neutral pH. Neutral pH is a pH from about 6.5 to about 7.5. The basic amino acid may be basic when it is the free acid form, or it may only be basic as the ester or amide form of the amino acid. Suitable basic amino acids that are basic in the free acid form include, but are not limited to, arginine, lysine, histidine, L-Arginine, D-Arginine, DL-Arginine, homoarginine, 3- and 4-substituted arginine analogs, N(delta)-methyl-L-arginine (deltaMA), L-canavanine, D-canavanine, DL-canavanine, protected and/or substituted analogs of canavanine, L-α-Amino-β-guanidinopropionic acid, γ-guanidinobutyric acid, citrulline, 3-guanidinopropionic
acid, 4-[[amino(imino)methyl]amino]butanoic acid, 6-[[amino(imino)methyl]amino]hexanoic acid, L-2-Amino-3-guanidinopropionic acid, L-Homoarginine, L-Arginine hydroxamate, Agmatine (CAS #: 2482-00-0), and NG-Methyl-L-arginine (CAS #: 53308-83-1). Other amino acids can be made into a basic amino acid if the acid group or groups are suitably protected. Suitable examples of basic amino acids that are esters include L-Arginine ethyl ester. Suitable examples of basic amino acids that are protected as amides include, but are not limited to, L-Arginimamide, L-Arginine N-ethylamide, and Arg-beta-Ala hydrochloride, (CAS #: 98957-79-0). In some embodiments, the basic amino acid comprises a guanidino group.

"Carbocycle" refers to a saturated or unsaturated hydrocarbon ring. Carbocycles are not aromatic. Carbocycles are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic carbocycles contain from about 4 to about 10 carbon atoms, suitably from 4 to 7 carbon atoms, or from 5 to 6 carbon atoms in the ring. Bicyclic carbocycles contain from 8 to 12 carbon atoms, suitably from 9 to 10 carbon atoms in the ring. Carbocycles may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Suitable carbocycle substituents include, but are not limited to, halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. Suitably, the carbocycle substituents are halo or haloalkyl. Suitable carbocycles include, but are not limited to, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

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

"Haloalkyl" refers to a straight, branched, or cyclic hydrocarbon substituted with one or more halo substituents. Suitably, the haloalkyl is C₁-C₁₂, or C₆-C₁₂, or C₃-C₃. Suitable halo substituents include fluoro and chloro. One suitable haloalkyl is trifluoromethyl.

"Heteroalkyl" refers to a saturated or unsaturated chain containing carbon and at least one heteroatom, wherein no two heteroatoms are adjacent. Heteroalkyl groups contain from 1 to 18 member atoms (carbon and heteroatoms) in the chain, or 1 to 12 member atoms, or 1 to 6 member atoms, or 1 to 4 member atoms. Heteroalkyl groups may be straight or branched. Suitably, the branched heteroalkyl may have one or two branches. Unsaturated heteroalkyl have one or more double bonds and/or one or more triple bonds. Suitably, heteroalkyl groups have one or two double bonds or one triple bond. Heteroalkyl groups may be unsubstituted or substituted with from 1 to about 4 substituents unless otherwise specified. Suitable heteroalkyl substituents include halo, aryl (e.g., phenyl, tolyl, alklyoxyphenyl, alklyoxycarbonylphenyl, haloxyphenyl), heterocycyl, heteroaryl. For example, alkyl chains substituted with the following substituents are heteroalkyl: alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy), aryloxy (e.g., phenoxy, chlorophenoxy, tolyoxy, methoxyphenox, benzylxoy, alklyoxycarbonylphenox, aclyoxyphenox), aclyoxy (e.g., propionylox, benzyloxy, acetoxy), carbamoylox, carboxy, mercapto, alklythio, aclythio, arythio (e.g., phenylthio, chlorophenylthio, alklyphenylthio, alkoxyphenylthio,
benzylthio, alkylxocarbonylphenylthio), amino (e.g., amino, mono- and di- \( \text{C}_1-\text{C}_3 \) alkylamino, methylphenylamino, methylbenzylamino, \( \text{C}_1-\text{C}_3 \) alkylamido, carbamamido, ureido, guanidino).

"Heteroatom" refers to a nitrogen, sulfur, or oxygen atom. Groups containing more than one heteroatom may contain different heteroatoms. As used herein, halogens are not considered heteroatoms.

"Heterocycle" refers to a saturated or unsaturated ring containing carbon and from 1 to about 4 heteroatoms in the ring, wherein no two heteroatoms are adjacent in the ring and no carbon in the ring that has a heteroatom attached to it also has a hydroxyl, amino, or thiol group attached to it. Heterocycles are not aromatic. Heterocycles are monocyclic, or are fused or bridged bicyclic ring systems. Monocyclic heterocycles contain from about 4 to about 10 member atoms (carbon and heteroatoms), suitably from 4 to 7 member atoms, or from 5 to 6 member atoms in the ring. Bicyclic heterocycles contain from 8 to 12 member atoms, suitably 9 or 10 member atoms in the ring. Heterocycles may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Suitably, the substituents are halo or haloalkyl. Suitable heterocycle substituents include: halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. Suitable heterocycles include, but are not limited to, piperzyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and piperdyl.

"Heteroaryl" refers to an aromatic ring system containing carbon and from 1 to about 4 heteroatoms in the ring. Heteroaryls are monocyclic or fused bicyclic ring systems. Monocyclic heteroaryls contain from about 5 to about 10 member atoms (carbon and heteroatoms), or from 5 to 7 member atoms, or from 5 to 6 member atoms in the ring. Bicyclic heteroaryls contain from 8 to 12 member atoms, or 9 or 10 member atoms in the ring. Heteroaryls may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Suitable heteroaryl substituents include: halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. Suitably, the substituents are halo, haloalkyl or phenyl. Suitable heteroaryls include, but are not limited to, benzothienyl, benzofuranyl, thiophenyl, thiazolo, purinyl, pyrimidyl, pyridyl, and furanyl.

"Lower alkyl" refers to an alkyl chain comprised of 1 to 4 carbon atoms, suitably 1 to 3 carbon atoms or 1 to 2 carbon atoms. Lower alkyl groups may be saturated or unsaturated and substituted or unsubstituted. Lower alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl.

"Lower heteroalkyl" refers to a heteroalkyl chain comprised of 1 to 4 member atoms. Lower heteroalkyl groups may be saturated or unsaturated and substituted or unsubstituted.
"Member atom" refers to a polyvalent atom (C, O, N, or S atom) in a chain or ring system that continues the chain or ring system. For example, in benzene the six carbon atoms are member atoms and the six hydrogen atoms are not member atoms.

"Phenyl" refers to a six-membered monocyclic aromatic ring which may or may not be substituted with from about 1 to about 4 substituents. The substituents may be substituted at the ortho, meta or para position on the phenyl ring, or any combination thereof. Suitable phenyl substituents include: halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof.

"Prostaglandin analog" refers to a compound that is designed to bind to a prostaglandin receptor. Prostaglandin analogs include protected prostaglandins, e.g. prostaglandins with esters or amides at the C1 position.

"Prostaglandin free acid" refers to a prostaglandin, prostaglandin analog or prostaglandin intermediate that has a carboxylic acid moiety at the C1 position.

"Prostaglandin intermediate" refers to a compound that is on the synthetic pathway to a compound that, in its active form, stimulates one or more of the prostaglandin receptors. Prostaglandin intermediates may be a protected prostaglandin or prostaglandin analog or they may have parts of their structures not yet attached. An example of a prostaglandin intermediate is a latanoprost free acid containing one or more silyl protecting groups on one or more of their alcohol moieties.

"Prostaglandin F analog" or "PGF analog" or "analog of PGF₂α," refers to a compound that is structurally similar to naturally occurring PGF₂α.

"Prostaglandin E analog" or "PGE analog" or "analog of PGE₂," or "analog of PGE₁," refers to a compound that is structurally similar to naturally occurring PGE₂.

"Prostaglandin D analog" or "PGD analog" or "analog of PGD₂," refers to a compound that is structurally similar to naturally occurring PGD₂.

"Protected" refers to a chemical structure wherein one or more of the chemically-sensitive groups in the molecule have been modified to reduce its activity and allow for better synthetic techniques to be used. In prostaglandins, typical groups where protection is used are the hydroxy groups and the carboxylic acid group. Less commonly protected are the ketones found in PGD and PGE analogues. Protecting groups vary but are generally found in the various editions of “Protecting Groups in Organic Synthesis” by Theadora Green.

"Unprotected" refers to a chemical structure that does not contain any groups that have been added to protect sensitive functional moieties such as hydroxy groups or carboxylic acid groups.

"Pharmaceutically acceptable carrier" refers to a carrier that is useful for the preparation of a pharmaceutical composition that is: generally compatible with the other
ingredients of the composition, not deleterious to the recipient, and neither biologically nor otherwise undesirable.

"A pharmaceutically acceptable carrier" includes both one and more than one carrier. Embodiments include carriers for topical, ocular, parenteral, intravenous, intraperitoneal intramuscular, sublingual, nasal and oral administration. "Pharmaceutically acceptable carrier" also includes agents for preparation of aqueous dispersions and sterile powders for injection or dispersions.

"Excipient" refers to a physiologically compatible additives useful in preparation of a pharmaceutical composition. Examples of pharmaceutically acceptable carriers and excipients can for example be found in Remington Pharmaceutical Science, 16th Ed.

"Therapeutically effective amount" refers to a dosage of the compounds or compositions effective for influencing, increasing, decreasing the activity of a receptor, in particular a prostaglandin receptor in a mammal. This term as used herein may also refer to an amount effective at bringing about a desired in vivo effect in a mammal, preferably, a human, such as reduction in intraocular pressure.

"Administering" refers to administration of the compounds as needed to achieve the desired effect.

"Eye disease" includes, but is not limited to, glaucoma, allergy, cancers of the eye, neurodegenerative diseases of the eye, and dry eye.

The term "contacting a cell" is used to mean contacting a cell in vitro or in vivo (i.e. within a subject, such as a mammal, including humans, rabbits, cats and dogs).

**Amino Acid Prostaglandin Salts**

The present invention is directed to novel amino acid salts of prostaglandin free acids. Suitable salts include those of Formula I below:

\[
\left[ A^{-} \right]^{+} \left[ \text{Amino Acid} \right]^{+}
\]

wherein \([A]^{-}\) is an anion of a prostaglandin free acid, and all optical isomers, diastereomers, enantiomers, solvates and hydrates thereof. In one embodiment, the stereochemistry at all stereocenters is that of the naturally-occurring amino acid and naturally-occurring prostaglandin.

In some embodiments, the amino acid is a basic amino acid.
In some embodiments, the amino acid prostaglandin salts according to the present invention comprise a prostaglandin free acid of **Formula II** shown below:

![Formula II](image)

or optical isomers, diastereomers, or enantiomers thereof;

wherein a and b are, independently, single, double or triple bonds;

wherein Q₁, Q₂, and Q₃ are independently selected from hydrogen or an alcohol protecting group;

wherein each R₁ is, independently selected from hydrogen or lower alkyl;

wherein Y is =O, -S-, -S(O), -SO₂-, -C(R³)₂-, -NR¹-, -CR²=CR²-, or -C=C-;

wherein Z is selected from hydrogen, carbocycle, aryl or heteroaryl;

wherein each R², if present, is independently selected from hydrogen, lower alkyl, alkoxy, or hydroxyl; and

wherein p, and q are independently an integer of from 0 to 4.

Suitably, no carbon atom in **Formula II** has two or more heteroatoms attached to it unless the two or more heteroatoms are member atoms in a heterocyclic ring system.

In **Formula II** above, the relative stereochemistry at C₆, C₉, and C₁₂ is as specified above. That is, the bond between C₇ and C₈ is in the α orientation, the alcohol (protected or unprotected) at C₉ is in the α orientation, and the bond between C₁₂ and C₁₃ is in the β orientation. The invention also includes optical isomers, diastereomers and enantiomers of the above structure. At all stereocenters where stereochemistry is not defined (e.g. C₁₁ and C₁₅), both epimers are envisioned. In some embodiments of the present invention, stereochemistry at all such stereocenters of the invention mimic that of naturally occurring PGF₂α.

In some embodiments, Q₁ is either H or an alcohol protecting group and Q₂ and Q₃ are alcohol protecting groups. In other embodiments, Q₁, Q₂, and Q₃ are all alcohol protecting groups and may be different alcohol protecting groups and may be the same alcohol protecting group.
Suitable prostaglandin free acids include bimatoprost free acid, fluprostenoil free acid, latanoprost free acid, tafluprost free acid and travoprost free acid.

Latanoprost

Latanoprost free acid

Bimatoprost

Bimatoprost free acid
travoprost

travoprost free acid

tafluprost

tafluprost free acid
The amino acid prostaglandin salts of the present invention are readily formulatable and recrystallizable. They generally are dry free-flowing powders with relatively low tackiness and thus are useful in manufacture. Suitably, the salts have a melting point of at least about 35°C or at least about 50°C.

Amino acid prostaglandin salts according to the present invention include, but are not limited to, those shown below:

7-((1R,2R,3R,5S)-3,5-dihydroxy-2-((S,E)-3-hydroxy-5-phenylpent-1- enyl)cyclopentyl)heptanoic acid, arginine salt:

7-((1R,2R,3R,5S)-3,5-dihydroxy-2-((R)-3-hydroxy-4-phenoxybutyl) cyclopentyl)heptanoate, arginine salt:
Arginyl (Z)-7-((1R,2R,3R,5S)-3,5-dihydroxy-2-((R,E)-3-hydroxy-4-phenoxynbut-1-enyl)cyclopentyl)hept-5-enoate:

Arginyl (Z)-7-((1R,2R,3R,5S)-2-((R,E)-4-(3-chlorophenoxyl)-3-hydroxybut-1-enyl)-3,5-dihydroxy cyclopentyl)hept-5-enoate:
Arginyl (Z)-7-((1R,2R,3R,5S)-3,5-dihydroxy-2-((R,E)-3-hydroxy-4-(3-(trifluoromethyl)phenoxy) but-1-enyl)cyclopentyl)hept-5-enoate

5


10

Arginyl 7-((1R,2R,3R,5S)-2-((R)-5-(2-fluorophenyl)-3-hydroxypent-4-ynyl)-3,5-dihydroxycyclopentyl) heptanoate
Arginyl 7-((1R,2R,3R,5S)-2-((R)-4-(2-fluorophenylthio)-3-hydroxybutyl)-3,5-dihydroxy
cyclopentyl)heptanoate

Arginyl (Z)-7-((1R,2R,3R)-3-hydroxy-2-((S,E)-3-hydroxy-5-phenylpent-1-enyl)-5-oxo
cyclopentyl)hept-5-enoate
Arginy l 7-((1R,2R,3R)-3-hydroxy-2-((S,E)-3-hydroxy-5-phenylpent-1-enyl)-5-oxocyclopentyl)heptanoate

PGE₁, arginine salt

PGE₂, arginine salt
PGD2 arginine salt:

Other prostaglandins and related compounds suitable for use in the present invention include, but are not limited to, those found in the following US and World Patents and patent applications, which are incorporated herein by reference.

1. 5-Thia-omega substituted phenyl-prostaglandin E derivatives, process for producing the same and drugs containing the same as the active ingredient. WO 00/3980.


3. Aromatic C_{16}-C_{20}-substituted tetrahydro prostaglandins useful as FP agonists WO 99/12898.


17. 162. Alcon Laboratories, Inc. (Sallee VL, Hellberg MR, Klimko PG) 15-Ketal prostaglandins for the treatment of glaucoma or ocular hypertension WO 98/20881.
18. 9-Oxa prostaglandin analogs as ocular hypotensives. WO 98/57942.
19. 15-Fluoro prostaglandins as ocular hypotensives WO 98/21181.
20. 11-Halo prostaglandins for the treatment of glaucoma or ocular hypertension WO 98/20880.
22. Prostaglandin product WO 00/3736.
23. Substituted tetrahydrofuran analogs of prostaglandins as ocular hypotensives WO 97/23223.
24. EP2-receptor agonists as agents for lowering intraocular pressure WO 95/19964.
27. Fluorinated prostaglandin derivatives and medicines WO 98/12175.

For example, such other prostaglandins and related compounds suitable for use in the present invention include, but are not limited to, the following.

Compounds (US 6462081) suitable for use in the invention include 5-thia-ω-substituted phenyl-prostaglandin E derivatives of the formula:
wherein, R\(^1\) is hydroxy, C1-6 alkyloxy or NR\(^6\)R\(^7\) (in which R\(^8\) and R\(^7\) is, each independently, hydrogen or C1-4 alkyl), R\(^2\) is oxo, halogen or O—COR\(^5\) (in which R\(^8\) is C1-4 alkyl, phenyl or phenyl(C1-4 alkyl)), R\(^3\) is hydrogen or hydroxy, R\(^4\) and R\(^4\)b is, each independently, hydrogen or C1-4 alkyl, R\(^5\) is phenyl substituted with the following substituent(s): i) 1 – 3 of C1-4 alkoxy-C1-4 alkyl, C2-4 alkenyloxy-C1-4 alkyl, C2-4 alkynloxy-C1-4 alkyl, C3-7 cycloalkyloxy-C1-4 alkyl, C3-7 cycloalkyl(C1-4 alkoxy)-C1-4 alkyl, phenyloxy-C1-4 alkyl, phenyl-C1-4 alkoxy-C1-4 alkyl, C1-4 alkylthio-C1-4 alkyl, C2-4 alkenylthio-C1-4 alkyl, C2-4 alkynylthio-C1-4 alkyl, C3-7 cycloalkylthio-C1-4 alkyl, C3-7 cycloalkyl (C1-4 alkylthio)-C1-4 alkyl, phenylthio-C1-4 alkyl or phenyl-C1-4 alkoxythio-C1-4 alkyl, ii) C1-4 alkoxy-C1-4 alkyl and C1-4 alkyl, C1-4 alkoxy-C1-4 alkyl and C1-4 alkoxy, C1-4 alkoxy-C1-4 alkyl and hydroxy, C1-4 alkoxy-C1-4 alkyl and halogen, C1-4 alkylthio-C1-4 alkyl and C1-4 alkyl, C1-4 alkylthio-C1-4 alkyl and C1-4 alkoxy, C1-4 alkylthio-C1-4 alkyl and hydroxy or C1-4 alkylthio-C1-4 alkyl and halogen, iii) haloalkyl or hydroxy-C1-4 alkyl, or iv) C1-4 alkyl and hydroxy; ----------- is single bond or double bond, with the proviso that when R\(^2\) is O—

Compounds (WO 99/12895) suitable for use in the invention include compunds of the formula:

\[
\begin{align*}
\text{wherein } & \text{R}_1 \text{ is CO}_2\text{H, C(O)NH}_2\text{OH, CO}_2\text{R}_5, \text{CH}_2\text{OH, S(O)}_2\text{R}_5, \text{C(O)NH}_2\text{R}_5, \text{C(O)NS}_2\text{R}_5, \text{or tetrazole; wherein } \text{R}_6 \text{ is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic } \text{ring, aromatic ring, or heteroaromatic ring. } \text{R}_2 \text{ is H or lower alkyl. } X \text{ is NR}_6\text{R}_7, \text{OR}_6, \text{SR}_6, \text{S(O)}_2\text{R}_6, \text{or S(O)}_2\text{R}_6; \text{wherein } \text{R}_6, \text{R}_7, \text{and R}_8 \text{ are independently selected from the group consisting of H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, and heteroaromatic ring; and wherein } \text{R}_9 \text{ is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. } \text{R}_3 \text{ and R}_4 \text{ are independently selected from the group consisting of H, CH}_3, \text{and C}_2\text{H}_5. \text{Preferred } \text{R}_3 \text{ and } \text{R}_4 \text{ are H. } Y \text{ is NR}_6\text{R}_7, \text{S(O)}_2, \text{or S(O)}_2\text{R}_6; \text{wherein } \text{R}_10 \text{ is H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring.}
\end{align*}
\]
Preferred $R_{10}$ is H and CH₃. Preferred Y is NH and S. Z is carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring.

Compounds (US 5977173) suitable for use in the invention include compounds of the formula:

![Chemical Structure](image)

wherein $R_1$ is CO₂H, C(O)NHOH, CO₂R₅, CH₂OH, S(O)₂R₅, C(O)NHR₅, C(O)NHS(O)₂R₅, or tetrazole; wherein $R_5$ is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. $R_2$ is H or lower alkyl. X is NR₆R₇, OR₈, SR₉, S(O)R₆, or S(O)₂R₆; wherein $R_6$, $R_7$ and $R_8$ are independently selected from the group consisting of H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, and heteroaromatic ring; and wherein $R_9$ is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. $R_3$ and $R_4$ are independently selected from the group consisting of H, CH₃, and C₂H₅. Y is NR₁₀, S, S(O), or S(O)₂; wherein $R_{10}$ is H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. Preferred $R_{10}$ is H and CH₃. Z is carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring.

Compounds (WO 99/12898) suitable for use in the invention include compounds of the formula:

![Chemical Structure](image)

wherein $R_1$ is CO₂H, C(O)NHOH, CO₂R₅, CH₂OH, S(O)₂R₅, C(O)NHR₅, C(O)NHS(O)₂R₅, or tetrazole; wherein $R_5$ is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. Preferred $R_5$ is H and CH₃.
ring, aromatic ring, or heteroaromatic ring. \( R_2 \) is H or lower alkyl. \( X \) is \( \text{NR}_6\text{R}_7, \text{OR}_9, \text{SR}_9, \text{S(O)}\text{R}_9, \text{S(O)}_2\text{R}_9, \text{or F} \); wherein \( \text{R}_6, \text{R}_7 \) and \( \text{R}_8 \) are selected independently from the group consisting of H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring; and wherein \( \text{R}_9 \) is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. \( \text{R}_3\) and \( \text{R}_4 \) are independently H, alkyl, hydroxyalkyl, alkoxyalkyl, \( \text{OR}_{10} \), or \( \text{SR}_{10} \), except that both \( \text{R}_3 \) and \( \text{R}_4 \) are not H; wherein \( \text{R}_{10} \) is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. \( \text{R}_{10} \) has from 1 to about 8 member atoms. \( Z \) is carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring.

Compounds (WO 99/12896) suitable for use in the invention include compounds of the formula:

![Chemical Structure](image-url)

wherein \( \text{R}_1 \) is \( \text{CO}_2\text{H}, \text{C(O)}\text{NHO}_2\), \( \text{CO}_2\text{R}_9 \), \( \text{CH}_2\text{OH} \), \( \text{S(O)}_2\text{R}_5 \), \( \text{C(O)}\text{NHR}_5 \), \( \text{C(O)}\text{NHS(O)}_2\text{R}_5 \), or tetrazole; wherein \( \text{R}_5 \) is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. \( \text{R}_2 \) is H or lower alkyl. \( X \) is \( \text{NR}_6\text{R}_7, \text{OR}_9, \text{SR}_9, \text{S(O)}\text{R}_9, \text{S(O)}_2\text{R}_9, \text{or F} \); wherein \( \text{R}_6, \text{R}_7, \) and \( \text{R}_8 \) are independently selected from the group consisting of H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, and heteroaromatic ring; and wherein \( \text{R}_9 \) is alkyl, heteroalkyl, carbocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. \( \text{R}_3\) and \( \text{R}_4 \) are independently H, \( \text{CH}_3 \), \( \text{C}_2\text{H}_5 \), \( \text{OR}_{10} \), \( \text{SR}_{10} \), or OH, except that both \( \text{R}_3 \) and \( \text{R}_4 \) are not OH; wherein \( \text{R}_{10} \) is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring, \( \text{R}_{10} \) having from 1 to about 8 member atoms. \( Y \) is \( (\text{CH}_2)_n \); \( n \) being an integer from 0 to about 3. \( Z \) is carbocyclic aliphatic ring, heterocyclic aliphatic ring, monocyclic heteroaromatic ring, or substituted phenyl when \( n \) is 0, 2, or 3; and \( Z \) is carbocyclic aliphatic ring, heterocyclic aliphatic ring, or substituted phenyl when \( n \) is 1.

Compounds (US 6048895) suitable for use in the invention include compounds of the formula:
wherein $R_1$ is CO$_2$H, C(O)NHOH, CO$_2$R$_5$, CH$_2$OH, S(O)$_2$R$_5$, C(O)NHR$_5$, C(O)NHS(O)$_2$R$_5$, or tetrazole; wherein $R_5$ is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. $R_2$ is H or lower alkyl. X is NR$_6$R$_7$, OR$_8$, SR$_9$, S(O)R$_9$, S(O)$_2$R$_9$, or F; wherein $R_6$, $R_7$ and $R_8$ are selected independently from the group consisting of H, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring; and wherein $R_9$ is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. $R_3$ and $R_4$ are independently H, alkyl, hydroxyalkyl, alkoxyalkyl, OR$_{10}$, or SR$_{10}$, except that both $R_3$ and $R_4$ are not H; wherein $R_{10}$ is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. $R_{10}$ has from 1 to about 8 member atoms. Z is carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring.

Compounds (US 5770759) suitable for use in the invention include 13,14-dihydro-15-keto-PGF compounds of the formula:

wherein C-2, -3 double bond may or may not be located; X is
one of four possibilities shown above. \( R_1 \) is a hydrogen atom, an alkyl, phenyl, benzoyl, hydroxyalkyl, alkoxyalkyl, trialkylsilyl, and tetrapyranyl group; \( R_2 \) is a hydrogen atom or a lower alkyl group; \( R_3 \) and \( R_3' \) are a hydroxyl, methyl or hydroxymethyl; \( R_4 \) and \( R_5 \) are the same or different, and signify a hydrogen atom, a lower alkyl or a halogen atom; and \( R_6 \) is either an alkyl group consisted of 4 to 9 carbons which may or may not be branched one, contain double bonds or may bear alkoky substituents or the group shown in the formula following:

\[
\begin{align*}
\text{CH}_2 & \quad \text{CH}_2 \\
6 & \quad 5 \\
\text{CH} & \quad \text{CH} \\
6 & \quad 5 \\
\end{align*}
\]

\( \text{CH} = \text{CH} \) or \( \text{C} \equiv \text{C} \)

(wherein \( Y \) indicates a single bond with C-16, or an oxygen atom; \( R_7 \) indicates a hydrogen or halogen atom or a halogenated alkyl); excepting the compound wherein \( R_1 \), \( R_2 \), \( R_4 \) and \( R_5 \) are simultaneously hydrogen atoms, \( R_6 \) is a n-Bu, \( R_3 \) and \( R_3' \) are both hydroxyls and C-2 and C-3 are singly bonded. \( X \) in the general fromula represents the four types of the partial structure illustrated above.

Compounds (WO 99/26629) suitable for use in the invention include compounds of the formula:
wherein the wavy bands indicate the α or β configuration, R is hydrogen or a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or ~ (CH₂)ₙR₁ wherein m is 0-10, and R₁ is an aliphatic ring having from about 3 to about 7 carbon atoms, or an aryl or heteroaryl ring having from about 4 to about 10 carbon atoms, e. g. R₁ may be cyclohexyl, phenyl, thienyl, pyridyl or furanyl, or a pharmaceutically acceptable salt thereof and the dashed bond represents either a single or double bond which may be in the cis or trans position. Compounds suitable for use in the invention also include compounds of the formula:

wherein R₂ is hydrogen or a lower alkyl radical and the other symbols are as defined above.

Compounds (US 6030999) suitable for use in the invention include compounds of the general formula:
wherein A represents the alicyclic ring C₆–C₁₂ and the bonds between the ring and the side chains represent the various isomers. In PGA, PGB, PGD, PGE and PGF, A has the formula:
The invention is based on the use of derivatives characterized by their omega chain and various modifications of the alpha chain is therefore possible still using the inventive
concept. The alpha chain could typically be the naturally occurring alpha chain, which is esterified to the structure:

\[
\text{COO } R_1
\]

wherein \( R_1 \) is an alkyl group, preferably with 1-10 carbon, especially 1-6 atoms, for instance methyl, ethyl, propyl, isopropyl, butyl, isobutyl, neopentyl or benzyl or a derivative giving the final substance equivalent properties as a glaucoma agent. The chain could preferably be a \( \text{C}_6-\text{C}_{10} \) chain which might be saturated or unsaturated having one or more double bonds, and allenes, or a triple bond and the chain might contain one or more substituents such as alkyl groups, alicyclic rings, or aromatic rings with or without hetero atoms. The omega chain is defined by the following formula:

\[
\begin{align*}
(13) & \quad (14) & \quad (15-24) \\
C & \quad B & \quad C & \quad D & \quad R_2
\end{align*}
\]

wherein \( C \) is a carbon atom (the number is indicated within parenthesis). \( B \) is a single bond, a double bond or a triple bond. \( D \) is a chain with 1-10, preferably 2-8, and especially 2-5, and particularly 3 carbon atoms, optionally interrupted by preferably not more than two hetero atoms (O, S, or N), the substituent on each carbon atom being H, alkyl groups, preferably lower alkyl groups within 1-5 carbon atoms, a carbonyl group, or a hydroxyl group, whereby the substituent on \( \text{C}_{15} \) preferably being a carbonyl group, or (R)-OH or (S)-OH; each chain \( D \) containing preferably not more than three hydroxyl groups or not more than three carbonyl groups. \( R_2 \) is a ring structure such as a phenyl group which is unsubstituted or has at least one substituent selected from \( \text{C}_1-\text{C}_6 \) alkyl groups, \( \text{C}_1-\text{C}_4 \) alkoxy groups, trifluoromethyl groups, \( \text{C}_1-\text{C}_3 \) aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl group; or an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole; or a cycloalkane or a cycloalkene with 3-7 carbon atoms in the ring, optionally substituted with lower alkyl groups with 1-5 carbon atoms.

Compounds (WO 99/25358) suitable for use in the invention include compounds of the general formula:
wherein the hatched segments represent a bond, the solid triangle represents a P bond, the wavy segment represents α or β bond, dashed lines represent a double bond or a single bond, R is a substituted heteroaryl radical having at least two pendant substituents selected from the group consisting of lower alkyl, e.g. C1 to C6 alkyl; halogen; trifluoromethyl; COR1; COCF3; SO2NR1; NO2; CN or at least one cyano substituent, i.e. CN; R1 is hydrogen or a lower alkyl radical having up to six carbon atoms, X is selected from the group consisting of -OR1 and -N(R1)2, Y is =O or represents 2 hydrogen radicals, and the 9, 11, or 15 lower alkyl esters thereof; provided, however, when said heteroaryl radical is a dichloro thienyl radical, said compound is not a 1-carboxylic acid or amide thereof. In particular, the substituents on the heteroaryl radical may be selected from the group consisting of lower alkyl, e.g. C1 to C6 alkyl; halogen, e.g. fluoro, chloro and bromo; trifluoromethyl (CF3); COR1, e.g. COCH3; COCF3; SO2NR1, e.g. SO2NH2; NO2; CN; etc.

Compounds (US 6037364) suitable for use in the invention include compounds of the general formula:

wherein the hatched segments represent α bonds, the solid triangle represents a β bond, the wavy segment represents α or β bond, dashed lines represent a double bond or a single bond, R is a substituted heteroaryl radical, R1 is hydrogen or a lower alkyl radical having up to six carbon atoms, X is selected from the group consisting of -OR1 and -N(R+1)2, Y is =O or represents 2 hydrogen radicals. In particular, the substituents on the heteroaryl radical may be selected from the group consisting of lower alkyl, e.g. C1 to C6 alkyl; halogen, e.g. fluoro, chloro and bromo; trifluoromethyl (CF3); COR1, e.g. COCH3; COCF3; SO2NR1, e.g. SO2NH2; NO2; CN; etc.
Compounds (US 5889052) suitable for use in the invention include compounds of the general formula:

wherein R₁ is H; C1-C12 straight-chain or branched alkyl; C1-C12 straight-chain or branched acyl; C3-C8 cycloalkyl; or a cationic salt moiety; R₂, R₃ are H, or C1-C5 straight-chain or branched alkyl; or R₂ and R₃ taken together may represent O; X is O, S, or CH₂; represents any combination of a single bond, or a cis or trans double bond for the alpha (upper) chain; and a single bond or trans double bond for the omega (lower) chain; R₉ is H, C1-C10 straight-chain or branched alkyl, or C1-C10 straight-chain or branched acyl; R₁₁ is H, C1-C10 straight-chain or branched alkyl, or C1-C10 straight-chain or branched acyl; Y is O, or H and OR₁₅ in either configuration wherein R₁₅ is H or C1-C10 straight-chain or branched alkyl, or C1-C10 straight-chain or branched acyl; and Z is Cl or CF₃; with the proviso that when R₂ and R₃ taken together represent O, then R₁ ≠ C1-C12 straight-chain or branched acyl; and when R₂ is R₃ is H, then R₁ ≠ a cationic salt moiety.

Compounds (WO 98/21182) suitable for use in the invention include compounds of the general formula:

wherein A = CO₂R, CONR¹R², CH₂OR³, or CH₂NR⁴R⁵; where R = H or cationic salt moiety, or CO₂R = pharmaceutically acceptable ester moiety; R¹, R² = same or different = H or alkyl; R³ = H, acyl, or alkyl; R⁴, R⁵ = same or different = H, acyl, or alkyl, with the proviso that if one of R⁴, R⁵ = acyl, then the other = H or alkyl; n = 0 or 2; L = OR⁶ in the α
configuration, where \( R^6 = \text{H, alkyl, or acyl}; \) or \( L = \text{halo in either configuration}; \) \( B = \text{O}, \)

\[
\begin{align*}
\text{R'}^1 &= \text{O} \quad \text{or} \\
\text{F} &= \text{O}
\end{align*}
\]

wherein \( R' = \text{H, alkyl, or acyl}; \) \( \cdots \) = single or trans double bond; \( D, D^1, \) taken together = \( \text{OCH}_2\text{CH}_2\text{O}; \) or \( D, D^1 = \text{different} = \text{H and OR}^6, \) where \( R^6 = \text{H, alkyl, or acyl}; \) or \( D = \text{fluorine in the \( \alpha \) configuration, and \( D^1 = \text{H in the \( \beta \) configuration; \( X = (\text{CH}_2)_m \) or (\text{CH}_2)_m\text{O}, where } m = 1-6; \) and \( Y = \text{a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, alkoxy, acyl, acyloxy, amino, alkylamino, acylamino, or hydroxy; or } X-Y = (\text{CH}_2)_p Y^1; \) where } p = 0-6; \) and

\[
Y^1 = \begin{array}{c}
\text{W} \\
\text{Z}
\end{array}
\]

wherein \( W = \text{CH}_2, \text{O, S(O)}_q, \text{NR}^6, \text{CH}_2\text{CH}_2, \text{CH=CH, CH}_2\text{O, CH}_2\text{S(O)}_q, \text{CH}=\text{N, or CH}_2\text{NR}^6; \)

where \( q = 0-2, \) and \( R^6 = \text{H, alkyl, or acyl}; \) \( Z = \text{H, alkyl, alkoxy, acyl, acyloxy, halo, trihalomethyl, amino, alkylamino, acylamino, or hydroxy; and } \cdots = \text{single or double bond; or } X-Y = \text{cyclohexyl; with the proviso that the following compounds of formula III be excluded: those wherein: } L = \text{OR}^6 \text{ in the } \alpha \text{ configuration, where } R^6 \text{ is as defined above; } B = \)

\[
\begin{align*}
\text{R'}^1 &= \text{O} \\
\text{O}
\end{align*}
\]

where \( R' = \text{as defined above}; \) \( \cdots = \text{trans double bond; } D, D^1 = \text{different} = \text{H and OR}^6, \) where \( R^6 \) is as defined above; \( X = \text{CH}_2\text{CH}_2 \) or \( \text{CH}_2\text{O}; \) and \( Y = \text{a phenyl ring, optionally substituted with halo.} \)

Compounds (US 5994397) suitable for use in the invention include compounds of the general formula:

\[
\begin{align*}
\text{R} &= \text{a pharmaceutically acceptable ester moiety, } \text{CO}_2\text{R'}, \text{CONR}^7\text{R}^8, \text{CH}_2\text{OR}^9, \text{or CH}_2\text{NR}^{10}\text{R}^{11}, \text{where } R' = \text{H or cationic salt moiety; } R^7 \text{ and } R^8 \text{ are the same or different} = \text{H or alkyl; } R^9 = \text{H, acyl, or alkyl; and } R^{10} \text{ and } R^{11} \text{ are the same or different} = \text{H, acyl, or alkyl; with the proviso that if one of } R^{10} \text{ and } R^{11} = \text{acyl, then the other} = \text{H or alkyl; } n=0 \text{ or } 2; \text{ G is:}
\end{align*}
\]
wherein Y is CH₂CH=CH (cis olefin), CH=CHCH₂ (cis olefin), or CH₂CH₂CH₂; Z is C≡C, trans CH=CH, or CH₂CH₂; Y² is halogen or alkoxy; X² is O, S, or CH₂; and A is cis CH=CH, CH₂CH₂, or C≡C; one of R² and R³ is H, and the other is F or OH, where the OH may be free or functionally modified; or R² and R³ taken together is OCH₂CH₂O or double bonded O (carbonyl); and R⁴ is cyclohexyl, linear or branched C₅–C₇ alkyl, or R⁵ wherein R⁵ is (CH₂)ₚXphenyl or (CH₂)ₚZ₂, where X is O or CH₂; m = 1–6; the phenyl is either unsubstituted or substituted with R⁶, where R⁶ is halogen, CH₃, CF₃, CN, OCH₃ or acetyl; p = 0–6; and Z² is

wherein W is O, CH₂, CH₂CH₂, or CH=CH; and R⁶ is as defined above; provided that when G is (i) then R⁴ = R⁶ and when G is (ii) or (iii) then R⁴ is cyclohexyl, linear or branched C₅–C₇ alkyl, and R², R³ are different = H and OH.
Compounds (WO 98/57930) suitable for use in the invention include compounds of the general formula:

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{formula1.png}
\end{center}}
\]

wherein \( R_1 = H; \) C1-C5 alkyl or C3-C6 cycloalkyl; a cationic salt moiety; \( A = \text{CH}_2\text{CH}=\text{CH} \) (cis olefin), \( \text{CH} = \text{CHCH}_2 \) (cis olefin), or \( \text{CH}_2\text{CH}_2\text{CH}_2\); \( Z = \text{C}=\text{C}, \) trans \( \text{CH} = \text{CH}, \) or \( \text{CH}_2\text{CH}_2\); one of \( R_2 \) and \( R_3 = \text{H}, \) and the other = \( \text{F} \) or \( \text{OH}, \) where the \( \text{OH} \) may be free or functionally modified; or \( R_2 \) and \( R_3 \) taken together = \( \text{OCH}_2\text{CH}_2\text{O} \) or double bonded \( O \) (carbonyl); and \( R_4 = (\text{CH}_2)_m\text{Xphenyl} \) or \( (\text{CH}_2)_p\text{Z}_q, \) where \( X = \text{O} \) or \( \text{CH}_2; \) \( m = 1-6; \) the phenyl is either unsubstituted or substituted with \( R_5, \) where \( R_5 = \text{halogen}, \) \( \text{CH}_3, \) \( \text{CF}_3, \) \( \text{CN}, \) \( \text{OCH}_3 \) or acetyl; \( p = 0-6; \) and \( \text{Z}_q \) is:

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{formula2.png}
\end{center}}
\]

wherein: \( W = \text{O}, \) \( \text{CH}_2, \) \( \text{CH}_2\text{CH}_2, \) or \( \text{CH} = \text{CH}; \) and \( R_5 \) is as defined above.

Compounds (US 6025392) suitable for use in the invention include compounds of the general formula:

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{formula3.png}
\end{center}}
\]

wherein \( R \) is pharmaceutically acceptable ester moiety, \( \text{CO}_2\text{R}^1, \) \( \text{CONR}^7\text{R}^8, \) \( \text{CH}_2\text{OR}^9, \) or \( \text{CH}_2\text{NR}^{10}\text{R}^{11}, \) where \( \text{R}^1 \) is H or cationic salt moiety; \( \text{R}^7 \) and \( \text{R}^8 \) are the same or different = H or alkyl; \( \text{R}^9 \) is H, acyl, or alkyl; and \( \text{R}^{10} \) and \( \text{R}^{11} \) are the same or different = H, acyl, or alkyl; with the proviso that if one of \( \text{R}^{10} \) and \( \text{R}^{11} = \text{acyl}, \) then the other is H or alkyl; \( n=0 \) or 2; \( G \) is:
wherein Y is cis CH₂CH=CH, cis CH=CHCH₂, or CH₂CH₂CH₂; Z is C≡C, trans CH=CH, or CH₂CH₂; R²⁵ is H, acyl or alkyl; one of R² and R³ is H, and the other is F or OH, where the OH may be free or functionally modified; or R² and R³ taken together is OCH₂CH₂O or double bonded O (carbonyl); and R⁴ is (CH₂)ₙXphenyl or (CH₂)ₙZ², where X is O or CH₂; m = 1-6; p = 0-6; and Z² is:

wherein W is O, CH₂, CH₂CH₂, or CH=CH; and wherein the phenyl component of (CH₂)ₙXphenyl and the six-membered ring component of Z² independently may be unsubstiuted or substituted with halogen, CH₃, CF₃, CN, OCH₃, or acetyl; with the proviso that when R²⁵ is H, then R⁴ is (CH₂)ₙZ² and the six-membered ring component of Z² is unsubstituted.

Compounds (WO 98/21180) suitable for use in the invention include compounds of the general formula:

wherein Y is C(O)NR₁R₂, CH₂OR₃, CH₂NR₁R₂, CO₂R₁, CO₂M, where M is a cationic salt moiety; R₁, R₂ (same or different) = H, C1-C6 alkyl or alkenyl, or C3-C6 cycloalkyl; R, R₃ (same or different) = C(O)R₄, or H, where R₄ = C1-C6 alkyl or alkenyl, or C3-C6 cycloalkyl; A = CH₂CH₂, cis or trans CH=CH, or C≡C; Z = CH₂CH₂, trans CH=CH; X = O, S(O)ₙ, (CH₂)ₙ, or CH₂O, where n = 0, 1, or 2; B = H and OH in either configuration, or a double bonded O; D = R₁, OR₁, halogen, S(O)ₙR₄, NO₂, NR₁R₂, or CF₃, where n = 0, 1, or 2, and R₁, R₂, and R₄ are as defined above; and m = 0, 1, or 2.
Compounds (WO 98/57930) suitable for use in the invention include compounds of the general formula:

\[
\text{O} \quad \text{A} \quad \text{CO}_2\text{R}_1
\]

\[
\text{Z} \quad \text{R}_2 \quad \text{R}_3
\]

wherein \( R_1 = \text{H}; \text{C}1-\text{C}5 \text{ alkyl or C}3-\text{C}6 \text{ cycloalkyl}; \) a cationic salt moiety; \( \text{A} \) is \( \text{CH}_2\text{CH}=\text{CH} \) (cis olefin), \( \text{CH}=\text{CH}\text{CH}_2 \) (cis olefin), or \( \text{CH}_2\text{CH}_2\text{CH}_2 \); \( \text{Z} \) is \( \text{C}=\text{C} \), trans \( \text{CH}=\text{CH} \), or \( \text{CH}_2\text{CH}_2 \); one of \( R_2 \) and \( R_3 \) is \( \text{H} \), and the other is \( F \) or \( \text{OH} \), where the \( \text{OH} \) may be free or functionally modified; or \( R_2 \) and \( R_3 \) taken together is \( \text{OCH}_2\text{CH}_2\text{O} \) or double bonded \( \text{O} \) (carbonyl); and \( R_4 \) is \( (\text{CH}_2)_m\text{Xphenyl} \) or \( (\text{CH}_2)_m\text{Z}^2 \), where \( X = \text{O} \) or \( \text{CH}_2 \); \( m = 1-6 \); the phenyl is either unsubstituted or substituted with \( R_5 \), where \( R_5 = \text{halogen, CH}_3, \text{CF}_3, \text{CN, OCH}_3 \) or acetyl; \( p = 0-6 \); and \( Z^2 \) is:

\[
\text{or}
\]

wherein \( W = \text{O}, \text{CH}_2, \text{CH}_2\text{CH}_2, \) or \( \text{CH}=\text{CH} \); and \( R_5 \) is as defined above.

Compounds (WO 99/32441) suitable for use in the invention include compounds of the general formula:

\[
\text{R}_2
\]

\[
\text{R}_3
\]

\[
\text{G} \quad (\text{CH}_2)_n\text{R}_1
\]

wherein \( R^1 \) is \( \text{CO}_2\text{R} \), \( \text{CONR}^4\text{R}^5 \), \( \text{CH}_2\text{OR}^6 \), or \( \text{CH}_2\text{NR}^7\text{R}^8 \); wherein \( R \) is \( \text{H} \) or cationic salt moiety, or \( \text{CO}_2\text{R} \) forms a pharmaceutically acceptable ester moiety; \( R^4, R^5 = \text{same or different} = \text{H} \) or alkyl; \( R^6 = \text{H}, \text{acyl}, \) or alkyl; \( R^7, R^8 = \text{same or different} = \text{H}, \text{acyl}, \) or alkyl; with the proviso that if one of \( R^7, R^8 = \text{acyl} \), then the other = \( \text{H} \) or alkyl; \( n = 0 \) or \( 2; G = \text{CH}_2 \) or \( \text{O} \); \( R^2, R^3 = \text{same or different} = \text{OH}, \text{acyloxy, alkoxy, carbonyl, halogen, H} \), with the
proviso that at least one of $R^3$, $R^2$ is OH, acyloxy, alkoxy, or carbonyl; ---- is single or non-cumulated double bond; one of A, B = H, the other = halo, OH, acyloxy, or alkoxy; or A-B = O(CH$_2$)$_2$O or double bonded O; X = (CH$_2$)$_q$ or (CH$_2$)$_p$O; where $q$ = 1-6; and Y is a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, alkoxy, acyl, acyloxy, amino, alkylamino, acylamino, or hydroxy; or X-Y = (CH$_2$)$_p$Y'; where $p$ = 0-6; and Y' is:

wherein W = CH$_2$, O, S(O)$_m$, NR$_6$, CH$_2$CH$_2$, CH=CH, CH$_2$O, CH$_2$S(O)$_m$, CH=N, or CH$_2$NR$_6$; where $m$ = 0-2, and $R^9$ = H, alkyl, or acyl; Z = H, alkyl, alkoxy, acyl, acyloxy, halo, trihalomethyl, amino, alkylamino, acylamino, or hydroxy; and ---- is single or double bond, or X-Y = cyclohexyl or cyclopentyl.

Compounds (WO 98/39293) suitable for use in the invention include compounds of the general formula:

wherein $R^1$ = CO$_2$R, CONR$_4$R$_6$, CH$_2$OR$_6$, or CH$_2$NR$_7$R$_8$; wherein: $R = H$ or cationic salt moiety, or CO$_2$R = pharmaceutically acceptable ester moiety; $R^4$, $R^5$ = same or different = H or alkyl; $R^6$ = H, acyl, or alkyl; $R^7$, $R^8$ = same or different = H, acyl, or alkyl; with the proviso that if one of $R^7$, $R^8$ = acyl then the other = H or alkyl; $n$ = 0 or 2; $R^2$, $R^3$ = same or different = H, alkyl, or acyl; ---- is single or non-cumulated double bond; B = H, and OH in either configuration, H and F in either configuration, double bonded O, or OCH$_2$CH$_2$O; X = (CH$_2$)$_q$ or (CH$_2$)$_p$O; where $q$ = 1-6; and Y = C1-6 alkyl group or phenyl ring optionally substituted with alkyl, halo, trihalomethyl, alkoxy, acyl, acyloxy, amino, alkyl amino, or hydroxy; or X-Y = (CH$_2$)$_p$Y'; where $p$ = 0-6; and Y' is:

36
wherein $W = \text{CH}_2$, O, S(O)$_m$, NR$^9$, CH$_2$CH$_2$, CH=CH, CH$_2$O, CH$_2$S(O)$_m$, CH=N, or CHNR$^5$; where $m = 0\text{--}2$, and $R^9 = \text{H}$, alkyl, or acyl; $Z = \text{H}$, alkyl, alkoxy, acyl, acyloxy, halo, trihalomethyl, amino, alkylamino, acylamino, or hydroxy; and ----- is single or double bond.

Compounds (WO 98/20881) suitable for use in the invention include compounds of the general formula:

\[
\begin{align*}
\text{R}^2 & \text{O} \\
\text{R}^3 & \text{O} \\
\text{R}^4 & \text{CH}_2(\text{H})_n\text{R}^1 \\
\text{X-Y} & \\
\end{align*}
\]

wherein $R^1 = \text{CO}_2\text{R}$, CONR$^4$R$^5$, CH$_2$OR$^6$, or CH$_2$NR$^7$R$^8$, wherein R = H or cationic salt moiety, or CO$_2$R = pharmaceutically acceptable ester moiety; $R^4$, $R^5$ = same or different = H or alkyl; $R^6 = \text{H}$, acyl, or alkyl; $R^7$, $R^8$ = same or different = H, acyl, or alkyl; with the proviso that if one of $R^7$, $R^8 = \text{acyl}$, then the other = H or alkyl; n = 0 or 2; $R^2 = \text{H}$, alkyl, or acyl; $R^3 = \text{H}$, halo, or OR$^9$; where $R^9 = \text{H}$, alkyl, or acyl; ----- is single or non-cumulated double bond, with the provisos that if a double bond is present between carbons 4 and 5, it is of the cis configuration; and that if a double bond is present between carbons 13 and 14, it is of the trans configuration; $X = (\text{CH}_2)_m$ or $(\text{CH}_2)_m\text{O}$, where $m = 1\text{--}6$; and $Y = \text{phenyl}$, optionally substituted with alkyl, halo, trihalomethyl, alkoxy, acyl, acyloxy, amino, alkylamino, acylamino, or hydroxy; or $X-Y = (\text{CH}_2)_n Y^1$; where p = 0--6; and $Y^1$ is

\[
\begin{align*}
\text{W} & \text{Z} \\
\text{or} & \\
\text{W} & \text{Z} \\
\end{align*}
\]

wherein $W = \text{CH}_2$, O, S(O)$_m$, NR$^{10}$, CH$_2$CH$_2$, CH=CH, CH$_2$O, CH$_2$S(O)$_m$, CH=N, or CH$_2$NR$^9$, where $q = 0\text{--}2$, and $R^{10} = \text{H}$, alkyl, or acyl; $Z = \text{H}$, alkyl, alkoxy, acyl, acyloxy, halo, trihalomethyl, amino, alkylamino, acylamino, or hydroxy; and ----- is single or double bond.

Compounds (WO 98/57942) suitable for use in the invention include compounds of the general formula:
wherein $R = \text{ophthalmically acceptable ester moiety, CO}_2R^1$, CONR$^7R^8$, CH$_2$OR$^9$, or CH$_2$NR$^{10}$R$^{11}$ wherein $R^1 = H$, a cationic salt moiety, or an ophthalmically acceptable ammonium moiety; $R^7$ and $R^8$ are the same or different = H or alkyl; $R^9 = H$, acyl, or alkyl; and $R^{10}$ and $R^{11}$ are the same or different = H, acyl, or alkyl; with the proviso that if one of $R^{10}$ and $R^{11} = \text{acyl}$, then the other = H or alkyl; n = 0 or 2; $G$ is:

![Chemical Structures]

wherein $Y = \text{cis CH}_2\text{CH}=\text{CH}$, cis CH=CHCH$_2$, or CH$_2$CH$_2$CH$_2$; $Z = \text{C}=\text{C}$, trans CH=CH, or CH$_2$CH$_2$; one of $Y^2$ and $Y^3 = H$, and the other = halogen or OH, where the OH may be free or functionally modified; $X^2 = \text{O}$, S, or CH$_2$; $A = \text{cis CH}=\text{CH}$, CH$_2$CH$_2$, or C=C ; and one of $Z^3$ and $Z^4 = H$, and the other = OH, where the OH may be free or functionally modified; or $Z^3$ and $Z^4$ taken together = double bonded O (carbonyl); one of $R^2$ and $R^3 = H$, and the other = F or OH, where the OH may be free or functionally modified; or $R^2$ and $R^3$ taken together = OCH$_2$CH$_2$O or double bonded O (carbonyl); and $R^4 = \text{cyclohexyl}, \text{linear or branched C5-C7 alkyl}$, or $R^5$, wherein $R^5 = (\text{CH}_2)_mX$phenyl or (CH$_2)_pZ^2$, where $X = \text{O}$ or CH$_2$; $m = 1-6$; the phenyl is either unsubstituted or substituted with $R^6$, where $R^6 = \text{halogen, CH}_3$, CF$_3$, CN, OCH$_3$ or acetyl; $p = 0-6$; and $Z^2$ is:
wherein \( W = O, \ CH_2, \ CH_2CH_2, \) or \( CH=CH; \) and \( R^6 \) is as defined above; provided that when \( G \) is (i) then \( R^4 = R^6; \) and when \( G \) is (ii) or (iii) then \( R^4 = \) cyclohexyl, linear or branched C5-C7 alkyl, and \( R^2, R^3 \) are different = H and OH.

Compounds (WO 98/21181) suitable for use in the invention include compounds of the general formula:

*Image of chemical structure* where \( R^1 = CO_2R, \ CONR^2R^5, \ CH_2OR^6, \) or \( CH_2NR^7R^8, \) where \( R = H \) or cationic salt moiety, or \( CO_2R = \) pharmaceutically acceptable ester moiety; \( R^4, R^6 = \) same or different = H or alkyl; \( R^6 = H, \) acyl, or alkyl; \( R^7, R^8 = \) same or different = H, acyl, or alkyl; with the proviso that if one of \( R^7, R^8 = \) acyl, then the other = H or alkyl; \( n = 0 \) or 2; ---- is single or non-cumulated double bond, with the provisos that a double bond between carbons 4 and 5 may not be of the trans configuration; and that a double bond between carbons 13 and 14 may not be of the cis configuration; \( R^2, R^3 = \) same or different = H, alkyl, or acyl; \( D, D^1 = \) different = H and fluorine; \( X = (CH_2)_q \) or \( (CH_2)_qO; \) where \( q = 1-6; \) and \( Y = \) a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, alkoxy, acyl, acyloxy, amino, alkylamino, acylamino, or hydroxy; or \( X-Y = (CH_2)_bY^1; \) where \( p = 0-6; \) and \( Y^1 \) is:

*Image of chemical structure* where \( W = CH_2, \ O, \ S(O)_m, NR^9, \ CH_2CH_2, \ CH=CH, CH_2O, \ CH_2S(O)_m, \ CH=N, \) or \( CH_2NR^8; \)

where \( m = 0-2, \) and \( R^9 = H, \) alkyl, or acyl; \( Z = H, \) alkyl, alkoxy, acyl, acyloxy, halo, trihalomethyl, amino, alkylamino, acylamino, or hydroxy; and ---- is single or double bond.

Compounds (WO 98/20880) suitable for use in the invention include compounds of the general formula:
wherein \( n = 0 \) or \( 2 \); \( R = \text{CO}_2R, \text{CONR}^4\text{R}^5, \text{CH}_2\text{OR}^6, \) or \( \text{CH}_2\text{NR}^7\text{R}^8 \); wherein \( R = \text{H} \) or cationic salt moiety, or \( \text{CO}_2R \) forms an ophthalmically acceptable ester moiety; \( R^4, R^5 = \text{same or different} = \text{H} \) or alkyl; \( R^6 = \text{H}, \text{acyl}, \text{or alkyl} \); \( R^7, R^8 = \text{same or different} = \text{H}, \text{acyl}, \text{or alkyl} \); with the proviso that if one of \( R^7, R^8 = \text{acyl} \), then the other = \( \text{H} \) or alkyl; \( Q = \text{halo} \); one of \( T^1, T^2 = \text{H} \), and the other = \( \text{OR} \), wherein \( R \) is as defined below; or \( T^1 \) and \( T^2 \) together = \( O \) (i.e., a carbonyl); \( R^2, R^3 = \text{same or different} = \text{H}, \text{alkyl}, \text{or acyl} \); ---- is single or non-cumulated double bond, with the provisos that a double bond between carbons 4 and 5 may not be of the trans configuration; and that a double bond between carbons 13 and 14 may not be of the cis configuration; \( X = (\text{CH}_2)_q \) or \( (\text{CH}_2)_q\text{O} \), where \( q = 1-6 \); and \( Y = \) a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, alkoxy, acyl, acyloxy, amino, alkylamino, acylamino, or hydroxy; or \( X-Y = (\text{CH}_2)_p\text{Y}^1 \); where \( p = 0-6 \); and \( \text{Y}^1 \) is:

\[
\begin{align*}
\text{W} & \quad \text{Z} \\
\text{or} & \\
\text{W} & \quad \text{Z}
\end{align*}
\]

wherein \( W = \text{CH}_2, \text{O, S(O)}_m, \text{NR}^9, \text{CH}_2\text{CH}_2, \text{CH} = \text{CH}, \text{CH}_2\text{O}, \text{CH}_2\text{S(O)}_m, \text{CH} = \text{N}, \) or \( \text{CH}_2\text{NR}^9 \); where \( m = 0-2 \), and \( R^9 = \text{H}, \text{alkyl}, \text{or acyl} \); \( Z = \text{H}, \text{alkyl}, \text{alkoxy}, \text{acyl, acyloxy, halo, trihalomethyl, amino, alkylamino, acylamino, or hydroxy} \); and ---- is single or double bond.

Compounds (WO 96/10407) suitable for use in the invention include compounds of the general formula:

\[
\begin{align*}
\text{OR} & \quad \text{OH} \\
\text{A} & \quad \text{X} \quad \text{Y} \\
\text{Z} & \quad \text{W}
\end{align*}
\]

wherein \( Y = \text{C(O)}\text{NR}_1\text{R}_2, \text{CH}_2\text{OR}_3, \text{CH}_2\text{NR}_1\text{R}_2, \text{CO}_2\text{R}_3, \text{CO}_2\text{M} \) where \( \text{M} \) is a cationic salt moiety; \( R_1, R_2 \) (same or different) = \( \text{H, C1-C6 alkyl or alkenyl, or C3-C6 cycloalkyl} \); \( R, R_3 \) (same or different) = \( \text{C(O)}\text{R}_4, \text{H} \); \( R_5 = \text{C1-C6 alkyl or alkenyl, or C3-C6 cycloalkyl} \); \( \text{X} = \text{O, S(O)}_n, \text{CH}_2; n = 0, 1, \text{or} 2 \); \( A = \text{CH}_2\text{CH}_2 \), cis or trans \( \text{CH} = \text{CH} \), or \( \text{C} = \text{C} \); \( Z = \text{CH}_2\text{CH}_2 \), trans
CH=CH, or C≡C; W = (CH₂)ₘ Aryl, (CH₂)ₘOAr where m = 1-6 and Aryl = phenyl, optionally substituted with halogen, hydroxy, alkoxy, haloalkyl, amino, or acylamino; or W is:

Wherein V = H, alkyl, halogen, hydroxy, alkoxy, acryloxy, haloalkyl, amino, acylamino, and L = CH₂, O, S(O)ₘ, CH₂CH₂, CH₂O, NR, CH=NR, CH₂S(O)ₘ, CH=CH, CH₂NR where m = 0-2 and R is as defined above.

Compounds (WO 97/23223) suitable for use in the invention include compounds of the general formula:

Wherein R = pharmaceutically acceptable ester moiety, CO₂R¹, CONR⁷R⁸, CH₂OR⁹, or CH₂NR¹⁰R¹¹ wherein R¹ = H or cationic salt moiety; R⁷ and R⁸ are the same or different = H or alkyl; R⁹ = H, acyl, or alkyl; and R¹⁰ and R¹¹ are the same or different = H, acyl, or alkyl; with the proviso that if one of R¹⁰ and R¹¹ = acyl, then the other = H or alkyl; n = 0 or 2; G is:

Wherein Y = CH₂CH=CH (cis olefin), CH=CHCH₂ (cis olefin), or CH₂CH₂CH₂; Z = C≡C, trans CH=CH, or CH₂CH₂; Y² = halogen or alkoxy; X² = O, S, or CH₂; and A = cis CH=CH, CH₂CH₂, or C≡C; one of R² and R³ = H, and the other = F or OH, where the OH may be
free or functionally modified; or $R^2$ and $R^3$ taken together = OCH$_2$CH$_2$O or double bonded O (carbonyl); and $R^4$ = cyclohexyl, linear or branched C5-C7 alkyl, or $R^5$; wherein $R^5$ = (CH$_2$)$_m$Xphenyl or (CH$_2$)$_p$Z, where X = O or CH$_2$; m = 1-6; the phenyl is either unsubstituted or substituted with $R^6$, wherein $R^6$ = halogen, CH$_3$, CF$_3$, CN, OCH$_3$ or acetyl; p = 0-6; and $Z^2$ is:

![Diagram](image)

wherein: $W$ = O, CH$_2$, CH$_2$CH$_2$, or CH=CH; and $R^6$ is as defined above; provided that when G is (i) then $R^4$ = $R^5$ and when G is (ii) or (iii) then $R^4$ = cyclohexyl, linear or branched C5-C7 alkyl, and $R^2$, $R^3$ are different = H and OH.

Compounds (WO 95/19964) suitable for use in the invention include compounds of the general formula:

![Diagram](image)

wherein the wavy bands indicate the α or β configuration, R is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or -(CH$_2$)$_m$R$_1$ wherein m is 0-10, and R$_1$ is an aliphatic ring having from about 3 to about 7 carbon atoms, or an aryl or heteroaryl ring having from about 4 to about 10 carbon atoms, e.g. R$_1$ may be cyclohexyl, phenyl, thiényl, pyridyl or furanyl, or a pharmaceutically acceptable salt thereof and the dashed bond represents either a single or double bond which may be in the cis or trans position. Compounds suitable for use in the invention also include compounds of the formula:
wherein R₂ is a lower alkyl radical and the other symbols are as defined above.

Compounds (WO 99/02165) suitable for use in the invention include compounds of the general formula:

wherein the wavy bonds represent the α or β configuration, and the dashed bonds represent a single bond, a triple bond or a double bond in the cis or trans configuration; R is hydrogen, saturated or unsaturated alkyl, preferably C1-10 alkyl, cycloalkyl, preferably C3-8 cycloalkyl, aryl, arylalkyl, preferably aryl-C2-5 alkyl, or heteroaryl; R1 is a saturated or unsaturated alkyl group having 2-5 carbon atoms, optionally interrupted by heteroatoms selected from oxygen, sulfur and nitrogen, cycloalkyl, preferably C3-7 cycloalkyl, cycloalkenyl, preferably C3-7 cycloalkenyl, aryl or heteroaryl; X is C-OH or C=O; R2 is hydrogen, hydroxy, methyl, ethyl, methoxy or OCOR4, where R4 is a straight or branched chain saturated or unsaturated alkyl group, preferably C1-10 alkyl, especially C1-6 alkyl, or a cycloalkyl, preferably C3-8 cycloalkyl, or aryl group; R3 is a straight or branched chain saturated or unsaturated alkyl group, preferably having 3-8 carbon atoms, especially 3-5 carbon atoms, optionally interrupted by one or more heteroatoms selected from oxygen, sulfur and nitrogen, each carbon atom optionally being substituted with a substituent selected from C1-5 alkyl, hydroxy and carbonyl groups, hydroxy and carbonyl preferentially being attached to carbon 15 of the prostaglandin structure, and said alkyl group optionally containing a cycloalkyl, preferably C3-8 cycloalkyl, aryl or heteroaryl group, which may be
mono- or independently multi-substituted with C1-3 alkyl, C1-3 alkoxy, hydroxy, nitro, trifluoromethyl or halogen; or a pharmaceutically acceptable salt or ester thereof.

Compounds (WO 98/50024, US 6037368) suitable for use in the invention include compounds of the general formula:

wherein either bond W or bond X can be a single or a double bond, Y is either (i) a hydroxyl group having either α or β orientation relative to the five-membered ring or (ii) a keto function at carbon 9, and Z is a hydrocarbon group which may be aliphatic (cyclic or non-cyclic), aromatic, or a combination of aliphatic and aromatic at carbon 16.

Compounds (WO 98/12175) suitable for use in the invention include compounds of the general formula:

wherein wherein A is an ethylene group, a vinylene group, an ethynylene group, -OCH₂- or -SCH₂-, R¹ is a substituted or unsubstituted C3-8 alkyl group, a substituted or unsubstituted C3-8 alkenyl group, a substituted or unsubstituted C3-8 alkynyl group, a substituted or unsubstituted C3-8 cycloalkyl group, a substituted or unsubstituted aralkyl group or a substituted or unsubstituted aryloxyalkyl group, each of R² and R³ which are independent of each other, is a hydrogen atom or an acyl group, or forms a single bond, X is -CH₂-, -O- or -S-, Z is -OR², -NHCOR², -NH₂SO₂R⁶, or -SR², or forms a single bond together with R² or R³, each of R⁴, R⁵, R⁶, and R⁷ which are independent of one another, is a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, an aryl group or an arylalkyl group, and a dual line consisting of solid and broken lines is a single bond, a cis-double bond or a trans-double bond.
Process for Making Amino Acid Prostaglandin Salts

It has surprisingly been discovered that the disadvantages of the difficult procedures used to solidify prostaglandin free acids can be overcome by making a basic amino acid salt of the free acid which can be easily crystallized and/or recrystallized as needed.

The general process for making the amino acid prostaglandin salts according to the present invention is depicted below in Scheme I:

\[
\begin{align*}
\text{CO} & \quad \text{OH} \\
R & \\
\downarrow & \\
\left[ \begin{array}{c}
\text{CO} \\
R
\end{array} \right] + & \\
\left[ \begin{array}{c}
\text{Basic Amino Acid}
\end{array} \right]^+ \\
\left[ \begin{array}{c}
\text{Basic Amino Acid}
\end{array} \right]
\end{align*}
\]

A prostaglandin free acid is reacted with an amino acid in an appropriate solvent to generate the amino acid prostaglandin salt. Solvents can vary but methanol, ethanol, water, THF are generally acceptable solvents.

The temperature of the reaction is suitably kept between -78°C and the ambient room temperature (about 20-25°C). Alternatively, the temperature is from about 0°C to about 20°C. The reaction is stirred for about 5 minutes to about 4 hours under these conditions until a precipitate forms, at which point the amino acid prostaglandin salt is removed by filtration.

The salt may be recrystallized by well-known methods in the art. One suitable method is to dissolve the salt in an alcohol, such as methanol, ethanol or isopropanol, and then add diethyl ether or ethyl acetate until the cloud point, then cool to create a precipitate. The nascent precipitate is then warmed to resolubilize the material and then slowly cooled to create crystals.
Prostaglandin free acids can be made from known starting materials and methods known to one of ordinary skill in the art. For example, many are also available from Cayman Chemical Company, Ann Arbor, MI. In addition, the following reference describes the synthesis of prostaglandins: Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. J. Am. Chem. Soc., 1969, 91, 5675 and Corey, E. J.; Schaaf, T. K.; Huber, W; Koelliker, U.; Weinshenker, N. M.; J. Am. Chem. Soc., 1970, 92, 397 (which is incorporated by reference herein).

Suitably, the prostaglandin free acid is a compound of Formula II:

![Formula II](image)

or optical isomers, diastereomers, or enantiomers thereof;
wherein a and b are, independently, single, double or triple bonds;
wherein Q₁, Q₂, and Q₃ are independently selected from hydrogen or an alcohol protecting group;
wherein each R₁ is, independently selected from hydrogen or lower alkyl;
wherein Y is –O–, –S–, –S(O), –SO₂–, –C(R₂)₂–, –NR₁–, –CR₂=CR₂–, or –C=C–;
wherein Z is selected from hydrogen, carbocycle, aryl or heteroaryl;
wherein each R₂, if present, is independently selected from hydrogen, lower alkyl, alkoxy, or hydroxyl; and
wherein p, and q are independently an integer of from 0 to 4.

**Synthesis of Prostaglandins**

The amino acid prostaglandin salts can be converted into prostaglandins or prostaglandin analogs in various ways. In one embodiment, the free acid is recovered by neutralizing the salt. The free acid can then be converted into a prostaglandin analog without isolation. Alternatively, the free acid can be isolated. Once the free acid is isolated, the free acid can be used itself or it can be converted to a prostaglandin analog. For example, the amino acid prostaglandin salts according to the present invention may be converted into prostaglandin analogs by neutralization of the salt, extraction of the free acid into an organic layer, leaving the amino acid behind in the aqueous layer. The organic layer can then, for example, be reacted with an additional reagent to provide a
prostaglandin ester. In another embodiment, the salt can be directly converted to a prostaglandin analog without isolation of the free acid.

In other embodiments, the salt may be directly converted to a prostaglandin analog by redissolving the salt in a suitable solvent, such as methanol, and adding an additional reagent to convert the salt directly into a prostaglandin analog. Suitable reagents include primary, allylic and benzylic bromides and primary and secondary iodides such as 2-iodopropane or compounds such as bromomethane or iodomethane which make the esters of the free acids, and primary or secondary amines which, in the presence of activating agents such as EDC, produce amides.

For example, the salt of a PGF analog may be dissolved in methanol or acetone and 2 equivalents of isopropyl iodide are added. A reaction ensues to make the isopropyl ester of the PGF analog. Isopropyl esters of prostaglandins are suitable for use in the treatment of glaucoma with some PGF analogs. In another embodiment, the salt of a PGF analog may be reacted directly with N-ethyl amine to produce an amide by dissolving the salt in DMF, then adding the amine and EDC, with a small amount of DMAP, and isolating the n-ethyl amide product.

If the prostaglandin free acid is desired, it can be recovered by neutralizing the salt. For example, the salt of a PGF analog is neutralized with a 3:1 mixture of saturated aqueous ammonium chloride and 1 molar hydrochloric acid, and then the organic layer, containing the free acid, can be separated from the aqueous layer containing the amino acid.

A prostaglandin intermediate salt may similarly be either directly converted to a prostaglandin analog by either isolation or by converting the salt directly into a prostaglandin analog or further intermediate thereof as is discussed above.

25 **Methods of Treatments Using Amino Acid Prostaglandin Salts**

The amino acid prostaglandin salts may be used to treat various conditions, including eye disorders, such as glaucoma, osteoporosis, improving nasal patency or treating neurogenic bladder. The amino acid prostaglandin salts of the present invention are also useful in a method of reducing or decreasing intraocular pressure.

In one embodiment, a cell is contacted with an amount of an amino acid prostaglandin salt effective to reduce intraocular pressure. The term “contacting a cell” is used to mean contacting a cell in *vitro* or in *vivo* (i.e., in a subject, such as a mammal, including humans, rabbits, cats and dogs). In some embodiments, the cell may be contacted as a result of administration of an amino acid prostaglandin salt to a subject. The term “administration” contemplates any route known to one of ordinary skill in the art, including, but not limited to, oral, topical, parenteral, injection, inhalation, implants, buccal and rectal.
An effective amount of an amino acid prostaglandin salt according to the present invention will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of treatment, the nature of concurrent therapy, the route of administration, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician. For example, an effective amount of the amino acid prostaglandin salts of the present invention for systemic administration is from about 0.01 to about 1000 μg/kg body weight, preferably from about 0.1 to about 100 μg/kg per body weight, most preferably from about 1 to about 50 μg/kg body weight per day. Transdermal dosages would be designed to attain similar serum or plasma levels, based upon techniques known to those skilled in the art of pharmacokinetics and transdermal formulations. Plasma levels for systemic administration are expected to be in the range of 0.01 to 100 ng/mL, more preferably from 0.05 to 50 ng/mL and most preferably from 0.1 to 10 ng/mL. While these dosages are based upon a daily administration rate, the amino acid prostaglandin salts of the present invention may also be administered at other intervals, such as twice per day, twice weekly, once weekly, or once a month. One of ordinary skill in the art would be able to calculate suitable effective amounts for other intervals of administration.

Compositions Comprising Amino Acid Prostaglandin Salts

In one embodiment, the amino acid prostaglandin salts are administered in a pharmaceutically acceptable composition, such as in or with a pharmaceutically acceptable carrier.

Compositions may include one or more of the isoforms of the amino acid prostaglandin salts of the present invention. When racemates exists, each enantiomer or diastereomer may be separately used, or they may be combined in any proportion. Where tautomers exist all possible tautomers are specifically contemplated.

Pharmaceutical compositions for use in accordance with the present invention may be formulated in a conventional manner using one or more physiologically acceptable carriers or excipients. Thus, the amino acid prostaglandin salts may be formulated for administration by, for example, solid dosing, eyedrop, in a topical oil-based formulation, injection, inhalation (either through the mouth or the nose), implants, or oral, buccal, parenteral or rectal administration. Techniques and formulations may generally be found in "Remington's Pharmaceutical Sciences", (Meade Publishing Co., Easton, Pa.).

The route by which the amino acid prostaglandin salts of the present invention (component A) will be administered and the form of the composition will dictate the type of carrier (component B) to be used. The composition may be in a variety of forms, suitable, for example, for systemic administration (e.g., oral, rectal, nasal, sublingual, buccal,
implants, or parenteral) or topical administration (e.g., local application on the skin, ocular, liposome or nanosphere delivery systems, or iontophoresis).

Carriers for systemic administration typically comprise at least one of a) diluents, b) lubricants, c) binders, d) disintegrants, e) colorants, f) flavors, g) sweeteners, h) antioxidants, j) preservatives, k) glidants, m) solvents, n) suspending agents, o) wetting agents, p) surfactants, combinations thereof, and others. All carriers are optional in the systemic compositions.

Ingredient a) is a diluent. Suitable diluents for solid dosage forms include sugars such as glucose, lactose, dextrose, and sucrose; diols such as propylene glycol; calcium carbonate; sodium carbonate; sugar alcohols, such as glycerin; mannitol; and sorbitol. The amount of ingredient a) in the systemic or topical composition is typically about 50 to about 90%.

Ingredient b) is a lubricant. Suitable lubricants for solid dosage forms are exemplified by solid lubricants including silica, talc, stearic acid and its magnesium salts and calcium salts, calcium sulfate; and liquid lubricants such as polyethylene glycol and vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma. The amount of ingredient b) in the systemic or topical composition is typically about 5 to about 10%.

Ingredient c) is a binder. Suitable binders for solid dosage forms include polyvinyl pyrrollidone; magnesium aluminum silicate; starches such as corn starch and potato starch; gelatin; tragacanth; and cellulose and its derivatives, such as sodium carboxymethylcellulose, ethyl cellulose, methylcellulose, microcrystalline cellulose, and sodium carboxymethylcellulose. The amount of ingredient c) in the systemic composition is typically about 5 to about 50%, and in ocular solid dosing forms up to 99%.

Ingredient d) is a disintegrant. Suitable disintegrants for solid dosage forms include agar, alginic acid and the sodium salt thereof, effervescent mixtures, croscarmelose, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, clays, and ion exchange resins. The amount of ingredient d) in the systemic or topical composition is typically about 0.1 to about 10%.

Ingredient e) for solid dosage forms is a colorant such as an FD&C dye. When used, the amount of ingredient e) in the systemic or topical composition is typically about 0.005 to about 0.1%.

Ingredient f) for solid dosage forms is a flavor such as menthol, peppermint, and fruit flavors. The amount of ingredient f), when used, in the systemic or topical composition is typically about 0.1 to about 1.0%.

Ingredient g) for solid dosage forms is a sweetener such as aspartame and saccharin. The amount of ingredient g) in the systemic or topical composition is typically about 0.001 to about 1%.
Ingredient h) is an antioxidant such as butylated hydroxyanisole ("BHA"), butylated hydroxytoluene ("BHT"), and vitamin E. The amount of ingredient h) in the systemic or topical composition is typically about 0.1 to about 5%.

Ingredient j) is a preservative such as benzalkonium chloride, methyl paraben and sodium benzoate. The amount of ingredient j) in the systemic or topical composition is typically about 0.001 to about 5%, suitably about 0.01 to about 5%.

Ingredient k) for solid dosage forms is a glidant such as silicon dioxide. The amount of ingredient k) in the systemic or topical composition is typically about 1 to about 5%.

Ingredient m) is a solvent, such as water, isotonic saline, ethyl oleate, glycerine, hydroxylated castor oils, alcohols such as ethanol, and phosphate buffer solutions. The amount of ingredient m) in the systemic or topical composition is typically from about 0 to about 100%.

Ingredient n) is a suspending agent. Suitable suspending agents include Avicel® RC-591 (from FMC Corporation of Philadelphia, PA) and sodium alginate. The amount of ingredient n) in the systemic or topical composition is typically about 1 to about 8%.

Ingredient o) is a surfactant such as lecithin, Polysorbate 80, and sodium lauryl sulfate, and the TWEEN® from Atlas Powder Company of Wilmington, Delaware. Suitable surfactants include those disclosed in the C.T.F.A. Cosmetic Ingredient Handbook, 1992, pp.587-592; Remington's Pharmaceutical Sciences, 15th Ed. 1975, pp. 335-337; and McCutcheon's Volume 1, Emulsifiers & Detergents, 1994, North American Edition, pp. 236-239. The amount of ingredient o) in the systemic or topical composition is typically about 0.1% to about 5%.

Although the amounts of components A and B in the systemic compositions will vary depending on the type of systemic composition prepared, the specific derivative selected for component A and the ingredients of component B, in general, system compositions comprise 0.01% to 50% of component A and 50 to 99.99% of component B.

Compositions for parenteral administration typically comprise A) 0.1 to 10% of the amino acid prostaglandin salts of the present invention and B) 90 to 99.9% of a carrier comprising a) a diluent and m) a solvent. In one embodiment, component a) comprises propylene glycol and m) comprises ethanol or ethyl oleate.

Compositions for oral administration can have various dosage forms. For example, solid forms include tablets, capsules, granules, and bulk powders. These oral dosage forms comprise a safe and effective amount, usually at least about 5%, and more particularly from about 25% to about 50% of component A). The oral dosage compositions further comprise about 50 to about 95% of component B), and more particularly, from about 50 to about 75%.
Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed. Tablets typically comprise component A, and component B a carrier comprising ingredients selected from the group consisting of a) diluents, b) lubricants, c) binders, d) disintegrants, e) colorants, f) flavors, g) sweeteners, k) glidants, and combinations thereof. Specific diluents include calcium carbonate, sodium carbonate, mannitol, lactose and cellulose. Specific binders include starch, gelatin, and sucrose. Specific disintegrants include alginic acid and croscarmelose. Specific lubricants include magnesium stearate, stearic acid, and talc. Specific colorants are the FD&C dyes, which can be added for appearance. Chewable tablets preferably contain g) sweeteners such as aspartame and saccharin, or f) flavors such as menthol, peppermint, fruit flavors, or a combination thereof.

Capsules (including implants, time release and sustained release formulations) typically comprise component A, and a carrier comprising one or more a) diluents disclosed above in a capsule comprising gelatin. Granules typically comprise component A, and preferably further comprise k) glidants such as silicon dioxide to improve flow characteristics. Implants can be of the biodegradable or the non-biodegradable type. Implants may be prepared using any known biocompatible formulation.

The selection of ingredients in the carrier for oral compositions depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this invention. One skilled in the art would know how to select appropriate ingredients without undue experimentation.

The solid compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that component A is released in the gastrointestinal tract in the vicinity of the desired application, or at various points and times to extend the desired action. The coatings typically comprise one or more components selected from the group consisting of cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, EUDRAGIT® coatings (available from Rohm & Haas G.M.B.H. of Darmstadt, Germany), waxes and shellac.

Compositions for oral administration can also have liquid forms. For example, suitable liquid forms include aqueous solutions, emulsions, suspensions, solutions reconstituted from non-effervescent granules, suspensions reconstituted from non-effervescent granules, effervescent preparations reconstituted from effervescent granules, elixirs, tinctures, syrups, and the like. Liquid orally administered compositions typically comprise component A and component B, namely, a carrier comprising ingredients selected from the group consisting of a) diluents, e) colorants, f) flavors, g) sweeteners, j) preservatives, m) solvents, n) suspending agents, and o) surfactants. Peroral liquid
compositions preferably comprise one or more ingredients selected from the group consisting of e) colorants, f) flavors, and g) sweeteners.

Other compositions useful for attaining systemic delivery of the subject amino acid prostaglandin salts include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as a) diluents including sucrose, sorbitol and mannitol; and c) binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose, and hydroxypropyl methylcellulose. Such compositions may further comprise b) lubricants, e) colorants, f) flavors, g) sweeteners, h) antioxidants, and k) glidants.

In one embodiment of the invention, the amino acid prostaglandin salts of the present invention are topically administered. Topical compositions that can be applied locally to the eye may be in any form known in the art, non-limiting Examples of which include solids, gelable drops, sprays, ointments, or a sustained or non-sustained release unit placed in the conjunctival cul-de-sac of the eye or another appropriate location.

Topical compositions that can be applied locally to the skin may be in any form including solids, solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like. Topical compositions comprise: component A, the amino acid prostaglandin salts described above, and component B, a carrier. The carrier of the topical composition preferably aids penetration of the amino acid prostaglandin salts into the eye. Component B may further comprise one or more optional components.

The exact amounts of each component in the topical composition depend on various factors. The amount of component A added to the topical composition is dependent on the IC50 of component A, typically expressed in nanomolar (nM) units. For example, if the IC50 of the medicament is 1 nM, the amount of component A will be from about 0.001 to about 0.3%. If the IC50 of the medicament is 10 nM, the amount of component A) will be from about 0.01 to about 1%. If the IC50 of the medicament is 100 nM, the amount of component A will be from about 0.1 to about 10%. If the IC50 of the medicament is 1000 nM, the amount of component A will be 1 to 100%, preferably 5% to 50%. If the amount of component A is outside the ranges specified above (i.e., lower), efficacy of the treatment may be reduced. One skilled in the art understands how to calculate and understand an IC50. The remainder of the composition, up to 100%, is component B.

The amount of the carrier employed in conjunction with component A is sufficient to provide a practical quantity of composition for administration per unit dose of the medicament. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references: Modern Pharmaceutics, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al.,

Component B may comprise a single ingredient or a combination of two or more ingredients. In the topical compositions, component B comprises a topical carrier. Suitable topical carriers comprise one or more ingredients selected from the group consisting of phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, symmetrical alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, dimethyl isosorbide, castor oil, combinations thereof, and the like. More particularly, carriers for skin applications include propylene glycol, dimethyl isosorbide, and water, and even more particularly, phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols and symmetrical alcohols.

The carrier of the topical composition may further comprise one or more ingredients selected from the group consisting of q) emollients, r) propellants, s) solvents, t) humectants, u) thickeners, v) powders, w) fragrances, x) pigments, and y) preservatives.

Ingredient q) is an emollient. The amount of ingredient q) in a skin-based topical composition is typically about 5 to about 95%. Suitable emollients include stearyl alcohol, glycercy monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate, and combinations thereof. Specific emollients for skin include stearyl alcohol and polydimethylsiloxane.

Ingredient r) is a propellant. The amount of ingredient r) in the topical composition is typically about 0 to about 95%. Suitable propellants include propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide, and combinations thereof.

Ingredient s) is a solvent. The amount of ingredient s) in the topical composition is typically about 0 to about 95%. Suitable solvents include water, ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulfoxide, dimethyl formamide, tetrahydrofuran, and combinations thereof. Specific solvents include water, ethyl alcohol and propylene glycol.

Ingredient t) is a humectant. The amount of ingredient t) in the topical composition is typically 0 to 95%. Suitable humectants include glycerin, sorbitol, sodium 2-pyrrolidone-
5-carboxylate, soluble collagen, dibutyl phthalate, gelatin, and combinations thereof. Specific humectants include glycerin.

Ingredient u) is a thickener. The amount of ingredient u) in the topical composition is typically about 0 to about 95%.

Ingredient v) is a powder. The amount of ingredient v) in the topical composition is typically 0 to 95%. Suitable powders include beta-cyclodextrins, hydroxypropyl cyclodextrins, chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically-modified magnesium aluminum silicate, organically-modified Montmorillonite clay, hydrated aluminum silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate, and combinations thereof. For ocular applications, specific powders include beta-cyclodextrin, hydroxypropyl cyclodextrin, and sodium polyacrylate. For gel dosing ocular formulations, sodium polyacrylate may be used.

Ingredient w) is a fragrance. The amount of ingredient w) in the topical composition is typically about 0 to about 0.5%, particularly, about 0.001 to about 0.1%. For ocular applications a fragrance is not typically used.

Ingredient x) is a pigment. Suitable pigments for skin applications include inorganic pigments, organic lake pigments, pearlescent pigments, and mixtures thereof. Inorganic pigments useful in this invention include those selected from the group consisting of rutile or anatase titanium dioxide, coded in the Color Index under the reference CI 77,891; black, yellow, red and brown iron oxides, coded under references CI 77,499, 77,492 and, 77,491; manganese violet (CI 77,742); ultramarine blue (CI 77,007); chromium oxide (CI 77,288); chromium hydrate (CI 77,289); and ferric blue (CI 77,510) and mixtures thereof.

The organic pigments and lakes useful in this invention include those selected from the group consisting of D&C Red No. 19 (CI 45,170), D&C Red No. 9 (CI 15,585), D&C Red No. 21 (CI 45,380), D&C Orange No. 4 (CI 15,510), D&C Orange No. 5 (CI 45,370), D&C Red No. 27 (CI 45,410), D&C Red No. 13 (CI 15,630), D&C Red No. 7 (CI 15,850), D&C Red No. 6 (CI 15,850), D&C Yellow No. 5 (CI 19,140), D&C Red No. 36 (CI 12,085), D&C Orange No. 10 (CI 45,425), D&C Yellow No. 6 (CI 15,985), D&C Red No. 30 (CI 73,360), D&C Red No. 3 (CI 45,430), the dye or lakes based on Cochineal Carmine (CI 75,570) and mixtures thereof.

The pearlescent pigments useful in this invention include those selected from the group consisting of the white pearlescent pigments such as mica coated with titanium oxide, bismuth oxychloride, colored pearlescent pigments such as titanium mica with iron oxides, titanium mica with ferric blue, chromium oxide and the like, titanium mica with an organic pigment of the above-mentioned type as well as those based on bismuth
oxychloride and mixtures thereof. The amount of pigment in the topical composition is typically about 0 to about 10%. For ocular applications a pigment is generally not used.

In a particularly preferred embodiment of the invention, topical pharmaceutical compositions for ocular administration are prepared typically comprising component A and B (a carrier), such as purified water, and one or more ingredients selected from the group consisting of y) sugars or sugar alcohols such as dextran, particularly mannitol and dextran 70, z) cellulose or a derivative thereof, aa) a salt, bb) disodium EDTA (Edetate disodium), and cc) a pH adjusting additive.

Examples of z) cellulose derivatives suitable for use in the topical pharmaceutical composition for ocular administration include sodium carboxymethylcellulose, ethylcellulose, methylcellulose, and hydroxypropyl-methylcellulose, particularly, hydroxypropyl-methylcellulose.

Examples of aa) salts suitable for use in the topical pharmaceutical composition for ocular administration include mono-, di- and trisodium phosphate, sodium chloride, potassium chloride, and combinations thereof.

Examples of cc) pH adjusting additives include HCl or NaOH in amounts sufficient to adjust the pH of the topical pharmaceutical composition for ocular administration to 5.0-7.5.

Component A may be included in kits comprising component A, a systemic or topical composition described above, or both; and information, instructions, or both that use of the kit will provide treatment for cosmetic and medical conditions in mammals (particularly humans). The information and instructions may be in the form of words, pictures, or both, and the like. In addition or in the alternative, the kit may comprise the medicament, a composition, or both; and information, instructions, or both, regarding methods of application of medicament, or of composition, preferably with the benefit of treating or preventing cosmetic and medical conditions in mammals (e.g., humans).

**EXAMPLES**

The following non-limiting examples further illustrate the processes of the present invention:

**Example 1**

**Preparation of latanoprost arginine salt (E1):**
To Latanoprost free acid (CAS # 41639-83-2) (1, 21.2 mg, 0.054 mmol) in MeOH/H₂O (4:1, 0.65 mL) was added L-Arginine (>98%, Sigma-Aldrich, St. Louis, MO). (72 mM solution in MeOH/H₂O [4:1]) (754 µL, 0.054 mmol) and the solution was stirred for 30 minutes. The solvents were evaporated then azeotroped with Et₂O and hexanes to give white crystalline Latanoprost-L-Arginine salt 2 (quantitative).

Recrystallization: To 26.5 mg of 1 in a 4 mL vial was added approx 0.5 mL of MeOH to dissolve, followed by 1.2-1.5 mL of Et₂O which precipitated out the product. The vial was put on ice for 5 min. The liquid was decanted and the solid dried to give pure 2, 22.9 mg.

Example 2

Using substantially the same procedure, but substituting PGE₂ free acid (CAS #: 363-24-6 ) for latanoprost free acid the arginine salt of PGE₂ can be made.

Examples 3-71

Arginine salts of the following commercially-available prostaglandins can be made by following the above procedure and substituting the appropriate prostaglandin free acid.

<table>
<thead>
<tr>
<th>Example</th>
<th>Free acid name</th>
<th>CAS #</th>
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<tr>
<td>3</td>
<td>8-iso Prostaglandin F2α</td>
<td>27415-26-5</td>
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<td>4</td>
<td>Prostaglandin D2</td>
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<td>5</td>
<td>Prostaglandin E1</td>
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<td>6</td>
<td>Prostaglandin F2α</td>
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<td>Prostaglandin D3</td>
<td>71902-47-1</td>
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<td>8</td>
<td>16,16-dimethyl Prostaglandin E2</td>
<td>39746-25-3</td>
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<tr>
<td>9</td>
<td>Butaprost (free acid)</td>
<td>433219-55-7</td>
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<td>10</td>
<td>Tafluprost (free acid)</td>
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<td>11</td>
<td>Bimatoprost (free acid)</td>
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<td>12</td>
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<td>13</td>
<td>Travoprost (free acid)</td>
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50  11-deoxy Prostaglandin F1α  37785-98-1
51  19(R)-hydroxy Prostaglandin F1α  81371-59-7
52  19(R)-hydroxy Prostaglandin F2α  64625-53-2
53  1α,1β-dihomo Prostaglandin F2α  57944-39-5
54  15(R),19(R)-hydroxy Prostaglandin F2α
55  16-phenoxy tetranor Prostaglandin F2α  51705-19-2
56  11-deoxy Prostaglandin F1β  37785-99-2
57  11-deoxy Prostaglandin F2β  37786-07-5
58  11β-Prostaglandin F1β  37785-86-7
59  15-keto Fluprostenol  
60  15(S)-15-methyl Prostaglandin F2α  35700-23-3
61  16,16-dimethyl Prostaglandin E1  41692-15-3
62  16,16-dimethyl Prostaglandin F2α  39746-23-1
63  17-trifluoromethylphenyl-13,14-dihydro trinor Prostaglandin F2α
64  17-trifluoromethylphenyl trinor Prostaglandin F2α  221246-34-0
65  Bimatoprost (free acid)-d4
66  (+)-Fluprostenol-d4
67  Prostaglandin B2  13367-85-6
68  Prostaglandin B3  36614-32-1
69  17-phenyl trinor Prostaglandin A2
70  (S)-AL 8810
71  Lubiprostone  136790-76-6

Example 72

To Latanoprost (free acid) (1, 21.2 mg, 0.054 mmol) in MeOH/H₂O (4:1, 0.65 mL) was added L-Arginine (72 mM solution in MeOH/H₂O [4:1]) (754 μL, 0.054 mmol) ((>98%) from Sigma-Aldrich Cat. A5006) and the solution was stirred for 30 minutes. The solvents were evaporated then azeotroped with Et₂O and hexanes to give white crystalline Latanoprost-L-Arginine salt 2 (quantitative).

Recrystallization: To 26.5 mg of 1 in a 4 mL vial was added approx 0.5 mL of MeOH to dissolve, followed by 1.2-1.5 mL of Et₂O which precipitated out the product. The
vial was put on ice for 5 min. The liquid was decanted and the solid dried to give pure 2, 22.9 mg.

**Example 73**

To travoprost free acid ((+)-fluprostolen free acid) 3 in MeOH/H₂O was added L-Arginine (>98%) (Sigma-Aldrich Cat. A5006) and the solution was stirred for 30 minutes. The solvents were evaporated then azeotroped with Et₂O and hexanes to give white crystalline travoprost-L-Arginine salt 4 (quantitative).

![Chemical Structure](image)

**Recrystallization:** To 4 is added enough MeOH to dissolve, and is followed by Et₂O to the cloud point, then warmed to redissolved and slowly cooled overnight. The liquid is decanted and the solid is dried to give pure 4.

**Example 74**

To travoprost free acid ((+)-fluprostolen free acid) 3 in MeOH/H₂O is added L-Homoarginine and the solution is stirred for 30 minutes. The solvents are evaporated then azeotroped with Et₂O and hexanes to give white crystalline travoprost-L-Homoarginine salt 5 (quantitative).

![Chemical Structure](image)

**Recrystallization:** To 5 was added enough EtOH to dissolve, followed by Et₂O which precipitated the product. The vial was put on ice for 5 min. The liquid was decanted and the solid dried to give the salt 5.

**Example 75**
Formulation of Liquid Compositions Comprising Present Compounds

A composition in liquid form is prepared by conventional methods, formulated as follows:

**Example 75: Preparation Table**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>PGF analog arginine salt</em></td>
<td>0-5 mg</td>
</tr>
<tr>
<td>PGE analog arginine salt</td>
<td>0-5 mg</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>5 mL</td>
</tr>
<tr>
<td>Ethyl alcohol</td>
<td>5 mL</td>
</tr>
</tbody>
</table>

1.0 mL of the above composition, when administered once a day, substantially increases the beauty and health of the mammalian skin onto which it is applied.

**Example 76**

Preparation of Skin Care Topical Product Comprising Present Compounds

A skin care, topical product is prepared by formulating a cream composition as illustrated below.

**Example 76: Preparation Table**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>PGF analog arginine salt</em></td>
<td>50 mg</td>
</tr>
<tr>
<td>Isopropyl isostereate</td>
<td>150 g</td>
</tr>
<tr>
<td>Polyacrylate 13/polyisobutene/Polyisorbate 20</td>
<td>35 g</td>
</tr>
<tr>
<td>Methyl paraben/propyl paraben</td>
<td>1 g</td>
</tr>
<tr>
<td>Distilled water</td>
<td>400 g</td>
</tr>
</tbody>
</table>

**Example 77**

Preparation of Skin Care Wipe Product Comprising Present Compounds

A skin care wipe product is prepared by impregnating such a wipe with the liquid composition of Example 75. Such a wipe may be impregnated by techniques known and readily available to those skilled in the art. Indeed, a preferred example of a wipe product is the Oil of Olay Facial Wipes, owned and distributed by The Procter and Gamble Company of Cincinnati, Ohio.

**Example 78**

Shampoos are made, comprising:
<table>
<thead>
<tr>
<th>Component</th>
<th>Ex. 78-1</th>
<th>Ex. 78-2</th>
<th>Ex. 78-3</th>
<th>Ex. 78-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonium Lauryl Sulfate</td>
<td>11.5 %</td>
<td>11.5 %</td>
<td>9.5 %</td>
<td>7.5 %</td>
</tr>
<tr>
<td>Ammonium Laureth Sulfate</td>
<td>4 %</td>
<td>3 %</td>
<td>2 %</td>
<td>2 %</td>
</tr>
<tr>
<td>Cocamide MEA</td>
<td>2 %</td>
<td>2 %</td>
<td>2 %</td>
<td>2 %</td>
</tr>
<tr>
<td>Ethylene Glycol Distearate</td>
<td>2 %</td>
<td>2 %</td>
<td>2 %</td>
<td>2 %</td>
</tr>
<tr>
<td>Cetyl Alcohol</td>
<td>2 %</td>
<td>2 %</td>
<td>2 %</td>
<td>2 %</td>
</tr>
<tr>
<td>Stearyl Alcohol</td>
<td>1.2 %</td>
<td>1.2 %</td>
<td>1.2 %</td>
<td>1.2 %</td>
</tr>
<tr>
<td>Glycerin</td>
<td>1 %</td>
<td>1 %</td>
<td>1 %</td>
<td>1 %</td>
</tr>
<tr>
<td>Polyquaternium 10</td>
<td>0.5 %</td>
<td>0.25 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Polyquaternium 24</td>
<td>-</td>
<td>-</td>
<td>0.5 %</td>
<td>0.25 %</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>0.1 %</td>
<td>0.1 %</td>
<td>0.1 %</td>
<td>0.1 %</td>
</tr>
<tr>
<td>Sucrose Polyesters of Cottonate Fatty Acid</td>
<td>3 %</td>
<td>3 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sucrose Polyesters of Behenate Fatty Acid</td>
<td>2 %</td>
<td>3 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Polydimethyl Siloxane</td>
<td>-</td>
<td>-</td>
<td>3 %</td>
<td>2 %</td>
</tr>
<tr>
<td>Cocaminopropyl Betaine</td>
<td>-</td>
<td>1 %</td>
<td>3 %</td>
<td>3 %</td>
</tr>
<tr>
<td>Lauryl Dimethyl Amine Oxide</td>
<td>1.5 %</td>
<td>1.5 %</td>
<td>1.5 %</td>
<td>1.5 %</td>
</tr>
<tr>
<td>Decyl Polyglucose</td>
<td>-</td>
<td>-</td>
<td>1 %</td>
<td>1 %</td>
</tr>
<tr>
<td>DMMDM Hydantoin</td>
<td>0.15 %</td>
<td>0.15 %</td>
<td>0.15 %</td>
<td>0.15 %</td>
</tr>
<tr>
<td>PGF analog arginine salt</td>
<td>-</td>
<td>0.2 %</td>
<td>0.2 %</td>
<td>-</td>
</tr>
<tr>
<td>PGE analog arginine salt</td>
<td>0.1 %</td>
<td>-</td>
<td>-</td>
<td>0.1 %</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 %</td>
</tr>
<tr>
<td>Phenoxethanol</td>
<td>0.5 %</td>
<td>0.5 %</td>
<td>0.5 %</td>
<td>0.5 %</td>
</tr>
<tr>
<td>Fragrance</td>
<td>0.5 %</td>
<td>0.5 %</td>
<td>0.5 %</td>
<td>0.5 %</td>
</tr>
<tr>
<td>Water</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
</tr>
</tbody>
</table>

A human subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 12 weeks, a shampoo described above is used daily by the subject. Approximately one liquid ounce of the formula is applied to the scalp and hair of the subject, left in place for not more than 5 minutes, then rinsed with water.

**Example 79**

Topical pharmaceutical compositions for lowering intraocular pressure are prepared by conventional methods and formulated as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (wt %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>PGF analog arginine salt</em></td>
<td>0.50</td>
</tr>
</tbody>
</table>
Dextran 70 0.1
Hydroxypropyl methylcellulose 0.3
Sodium Chloride 0.77
Potassium chloride 0.12
Disodium EDTA 0.05
Benzalkonium chloride 0.01
HCl and/or NaOH pH 7.0-7.2
Purified water q.s. to 100%

A compound according to this invention is used as the PF analog arginine salt. When the composition is topically administered to the eyes as a 40 microliter drop instilled into the affected eye once daily, the above composition decreases intraocular pressure in a patient suffering from glaucoma.

**Example 80**

Example 79 is repeated using a PGE analog arginine salt according to this invention. When administered as a drop twice per day, the above composition substantially decreases intraocular pressure.

**Example 81**

Topical pharmaceutical compositions for nasal sprays are prepared by conventional methods and formulated as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (wt %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGF analog arginine salt</td>
<td>0.1-0.50</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose</td>
<td>0.0-0.3</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>0.61</td>
</tr>
<tr>
<td>EDTA</td>
<td>0.05</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td>0.01</td>
</tr>
<tr>
<td>HCl and/or NaOH to pH 7.0-7.2</td>
<td></td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s. to 100%</td>
</tr>
</tbody>
</table>

**Example 82**

Topical pharmaceutical compositions for instillation, e.g., into a bladder are prepared by conventional methods and formulated as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (wt %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGF analog arginine salt</td>
<td>0.1-0.50</td>
</tr>
<tr>
<td>EDTA</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Example 83

To 1.0 gram of Latanoprost L-arginine salt (2) in MeOH/H₂O (4:1, 20 mL) is added 2.01 equivalents of isopropyl iodide (99%, Cat #148938, Sigma-Aldrich, St. Louis, MO). and the solution is stirred overnight. Saturated aqueous ammonium acetate is added along with ethyl acetate and the layers are separated. The organic layer is separated, and the solvents removed in vacuo, and the material is chromatographed to give latanoprost as the isopropyl ester (6).

Example 84

The procedure of example 83 is repeated substituting fluprostanol for latanoprost and methyl iodide for isopropyl iodide. Isolated is fluprostanol methyl ester (7)

Example 85
To 1.0 gram of Arginyi 7-(((1R,2R,3R,5S)-2-((R)-4-(2-fluorophenylthio))-3-hydroxybutyl)-3,5-dihydroxy cyclopentyl)heptanoate (8) in MeOH/H₂O (4:1, 20 mL) is added, dropwise with cooling, at least 5 equivalents of a 3:1 mixture of saturated aqueous ammonium chloride and 1 M hydrochloric acid (Sigma-Aldrich, St. Louis, MO), and the solution is stirred for 15 minutes. Saturated aqueous sodium chloride is added along with ethyl acetate. The organic layer is separated; is washed again with brine; the solvents removed in vaccuo, and the material chromatographed to give the free acid, 7-(((1R,2R,3R,5S)-2-((R)-4-(2-fluorophenylthio))-3-hydroxybutyl)-3,5-dihydroxy cyclopentyl)heptanoic acid (9).

Example 86

To 1.0 gram of bimataprost arginine salt (9) in DMF (20 mL) is added 2.01 equivalents of 2M ethyl amine solution in THF (Cat #395072, Sigma-Aldrich, St. Louis, MO) and 1.5 eq of EDC. and the solution is stirred overnight. Added is at least 5 equivalents of a 3:1 mixture of saturated aqueous ammonium chloride and 1 M hydrochloric acid (Sigma-Aldrich, St. Louis, MO), and the solution is extracted with ethyl acetate, washed and purified. Isolated is bimataprost N-ethyl amide (10)
Example 87

To 1.0 gram of bimataprost arginine salt (9) is added at least 5 equivalents of a 3:1 mixture of saturated aqueous ammonium chloride and 1 M hydrochloric acid (Sigma-Aldrich, St. Louis, MO), and the solution is extracted with diethyl ether. The organic layer is then separated, and added are: 20 mL of DMF, 2.01 equivalents of 2M ethyl amine solution in THF (Cat #395072, Sigma-Aldrich, St. Louis, MO), 1.5 eq of EDC and 0.2 eq of DMAP, and the solution is stirred overnight. Then added is at least 5 equivalents of a 3:1 mixture of saturated aqueous ammonium chloride and 1 M hydrochloric acid (Sigma-Aldrich, St. Louis, MO), and the solution is extracted with ethyl acetate, washed and purified. Isolated is bimataprost N-ethyl amide (10)

Example 88

White crystalline Latanoprost-L-Arginine salt 2 was prepared as described in Example 1. Latanoprost-L-Arginine salt 2 was recrystallized by dissolving the salt in 10 volumes of ethanol (under nitrogen) and cooling the solution to approximately -40°C. 30 volumes of methyl tert-butyl ether (MTBE) were added slowly to the solution while stirring gently. After the addition was complete, the mixture was stirred for a short period of time at approximately -40°C. Stirring was halted and the salt was allowed to settle. Most of the supernatant was removed by suction using a 100 mL pipet. 20 volumes of (1:3) ethanol:MTBE was added to the remaining mixture in the flask and stirred at approximately -40°C for a few minutes. Stirring was halted and the salt was allowed to settle. Most of the supernatant was removed by suction using a 100 mL pipet. 20 volumes of MTBE was added to the remaining mixture and stirred at approximately -40°C for a few minutes. Stirring was halted and the salt was allowed to settle. Most of the supernatant was removed by suction using a 100 mL pipet. 20 volumes of MTBE was added to the remaining mixture and stirred at approximately -40°C for a few minutes. The mixture was filtered and the solid was washed with 10 volumes of MTBE. The solid was placed a crystallizing dish in the vacuum oven under hi vac for drying.

Images of the recrystallized Latanoprost-L-Arginine salt 2 were taken using a compound microscope and camera and are presented in Figures 1-10. The images in Figures 4-6 were taken at 40x magnification, and the images in Figures 1-3 and 7-10 were
taken at 400x magnification. The crystals became more spherical over time, which may have indicated the uptake of water.
Claims

1. An amino acid salt of a prostaglandin free acid.

2. The salt according to claim 1, wherein the salt has a melting point of at least about 35°C.

3. The salt according to claim 1, wherein the amino acid is a basic amino acid.

4. The salt according to claim 1, wherein the prostaglandin free acid is a FP receptor ligand.

5. The salt according to claim 1, wherein the prostaglandin free acid is an EP receptor ligand.

6. The salt according to claim 1, wherein the amino acid comprises a guanidine group.

7. The salt according to claim 1, wherein the prostaglandin free acid is a compound according to Formula (II):

![Chemical Structure](image)

optical isomers, diastereomers, or enantiomers thereof;

wherein a and b are independently, single, double or triple bonds;

wherein Q₁, Q₂ and Q₃ are independently selected from hydrogen or alcohol protecting group;
wherein each $R^1$ is independently selected from hydrogen or lower alkyl;

wherein $Y$ is $-O-$, $-S-$, $-S(O)-$, $-\text{SO}_2-$, $-\text{C}(R^2)_2-$, $-\text{NR}^1-$, $-\text{CR}^2=\text{CR}^2-$, or $-\text{C}=\text{C}-$;

wherein $Z$ is selected from hydrogen, carbocycle, aryl, or heteroaryl;

wherein each $R^2$, if present, is independently selected from hydrogen, lower alkyl, alkoxy or hydroxyl; and

wherein $p$ and $q$ are independently an integer from 0 to 4.

8. The salt according to claim 7, wherein $Z$ is bicyclic.

9. The salt according to claim 7, wherein $Z$ is substituted.

10. The salt according to claim 7, selected from the group consisting of

$$7-\text{((1R,2R,3R,5S)-3,5-dihydroxy-2-((S,E)-3-hydroxy-5-phenylpent-1-enyl)cyclopentyl)heptanoic acid, arginine salt:}$$

$$7-\text{((1R,2R,3R,5S)-3,5-dihydroxy-2-((R)-3-hydroxy-4-phenoxbutyl) cyclopentyl)heptanoate, arginine salt:}$$
Arginyloxy (Z)-7-((1R,2R,3R,5S)-3,5-dihydroxy-2-((R,E)-3-hydroxy-4-phenoxybut-1-enyl) cyclopentyl) hept-5-enoate:
Arginy1 (Z)-7-((1R,2R,3R,5S)-3,5-dihydroxy-2-((R,E)-3-hydroxy-4-((3-(trifluoromethyl)phenoxy)but-1-enyl)cyclopentyl)hept-5-enoate

\[
\text{Arginy1 (Z)-7-((1R,2R,3R,5S)-3,5-dihydroxy-2-((R,E)-4-(2-fluorophenoxy)-3-hydroxybut-1-enyl)-3,5-dihydroxycyclopentyl)hept-5-enoate}
\]

Arginyl 7-((1R,2R,3R,5S)-2-((R)-5-(2-fluorophenyl)-3-hydroxypent-4-ynyl)-3,5-dihydroxycyclopentyl) heptanoate
Arginyl 7-((1R,2R,3R,5S)-2-((R)-4-(2-fluorophenylthio)-3-hydroxybutyl)-3,5-dihydroxy cyclopentyl)heptanoate

Arginyl (Z)-7-((1R,2R,3R)-3-hydroxy-2-((S,E)-3-hydroxy-5-phenylpent-1-enyl)-5-oxo cyclopentyl)hept-5-enoate
Arginyl 7-((1R,2R,3R)-3-hydroxy-2-((S,E)-3-hydroxy-5-phenylpent-1-enyl)-5-oxocyclopentyl)heptanoate

\[
\text{PGE}_1, \text{ arginine salt}
\]

\[
\text{PGE}_2, \text{ arginine salt}
\]

or
11. The salt according to claim 1, wherein the prostaglandin free acid is tafluprost free acid.

12. The salt according to claim 1, wherein the prostaglandin free acid is bitamoprost free acid.

13. The salt according to claim 1, wherein the prostaglandin free acid is latanoprost free acid.

14. The salt according to claim 1, wherein the prostaglandin free acid is fluprostfenol free acid.

15. The salt according to claim 1, wherein the salt is a product of a reaction between a prostaglandin free acid and an amino acid.

16. A pharmaceutical composition comprising a salt according to claim 1 and a pharmaceutically acceptable carrier.

17. A method of making an amino acid salt of a prostaglandin free acid comprising reacting a prostaglandin free acid with a basic amino acid to form an amino acid salt of prostaglandin free acid.

18. A method of making a prostaglandin analog comprising:

reacting a prostaglandin free acid with a basic amino acid to form a salt; and

converting the salt to a prostaglandin analog.
19. The method of claim 18, wherein the prostaglandin analog is an ester.

20. The method of claim 18, wherein the prostaglandin analog is an amide.

21. The method of claim 18, wherein the prostaglandin analog binds to the prostaglandin F receptor.

22. The method of claim 18, wherein the basic amino acid comprises a guanidino group.

23. A method of making a prostaglandin analog comprising:

reacting a prostaglandin free acid with a basic amino acid to form a salt;
neutalizing the salt to recover the prostaglandin free acid; and
converting the prostaglandin free acid to a prostaglandin analog.

24. The method of claim 23, wherein the prostaglandin analog is an ester.

25. The method of claim 23, wherein the prostaglandin analog is an amide.

26. The method of claim 23, wherein the prostaglandin analog binds to the prostaglandin F receptor.

27. The method of claim 23, wherein the basic amino acid comprises a guanidino group.

28. A method of making a prostaglandin comprising

reacting a prostaglandin free acid with a basic amino acid to form a salt; and
converting the salt to a prostaglandin.

29. The method of claim 28, wherein the prostaglandin binds to the prostaglandin F receptor.

30. The method of claim 28, wherein the basic amino acid comprises a guanidino group.

31. A method of treating glaucoma, or other eye disease comprising administering to a subject in need thereof an effective amount of a salt according to claim 1.
32. A method of improving nasal patency or treating neurogenic bladder comprising administering to a subject in need thereof an effective amount of a salt according to claim 1.

33. A method of treating osteoporosis comprising administering to a subject in need thereof an effective amount of a salt according to claim 1.

34. A method of treating skin disorders, respiratory disorders, circulatory disorders, gastrointestinal disorders, hair loss or fertility control comprising administering to a subject in need thereof an effective amount of a salt according to claim 1.

35. A method of reducing ocular pressure comprising contacting a cell with an amount of a salt according to claim 1 effective to reduce ocular pressure.

36. The method of claim 35, wherein the cell is in a subject.

37. An amino acid prostaglandin free acid salt, wherein the amino acid is selected from the group consisting of arginine, homoarginine, N(delta)-methyl-L-arginine, L-canavanine, D-canavanine, DL-canavanine, L-α-amino-β-guanidinopropionic acid, γ-guanidinobutyric acid, and citrulene; and wherein the prostaglandin free acid is selected from the group consisting of latanoprost free acid, travoprost free acid, fluprosteno free acid, tafluprost free acid, and bitamoprost free acid.

38. The salt according to claim 1, wherein the amino acid is arginine.

39. The salt according to claim 2, wherein the prostaglandin free acid is travoprost free acid.

40. The salt according to claim 2, wherein the prostaglandin free acid is fluprosteno free acid.

41. The salt according to claim 2, wherein the prostaglandin free acid is tafluprost free acid.

42. The salt according to claim 2, wherein the prostaglandin free acid is bitamoprost free acid.

43. An amino acid prostaglandin free acid salt, wherein the prostaglandin free acid is latanoprost free acid and the amino acid is arginine.

44. A pharmaceutical composition comprising a salt according to claim 1 and a pharmaceutically acceptable carrier.
45. A method of making a prostaglandin free acid salt comprising reacting a mixture comprising a prostaglandin free acid selected from the group consisting of latanoprost free acid, travoprost free acid, fluprostenol free acid, tafluprost free acid, and bitamoprost free acid with an amino acid selected from the group consisting of arginine, homoarginine, N(delta)-methyl-L-arginine, L-canavanine, D-canavanine, DL-canavanine, L-\(\alpha\)-amino-\(\beta\)-guanidinopropionic acid, \(\gamma\)-guanidinobutyric acid, and citrulene to form a salt.

46. A method of making a prostaglandin analog comprising:

reacting a prostaglandin free acid selected from the group consisting of latanoprost free acid, travoprost free acid, fluprostenol free acid, tafluprost free acid, and bitamoprost free acid with an amino acid selected from the group consisting of arginine, homoarginine, N(delta)-methyl-L-arginine, L-canavanine, D-canavanine, DL-canavanine, L-\(\alpha\)-amino-\(\beta\)-guanidinopropionic acid, \(\gamma\)-guanidinobutyric acid, and citrulene to form a salt; and

converting the salt to a prostaglandin analog.

47. The method of claim 10, wherein the prostaglandin analog is an ester.

48. The method of claim 10, wherein the prostaglandin analog is an amide.

49. The method of claim 10, wherein the prostaglandin analog binds to the prostaglandin F receptor.

50. A method of making a prostaglandin analog comprising:

reacting a prostaglandin free acid selected from the group consisting of latanoprost free acid, travoprost free acid, fluprostenol free acid, tafluprost free acid, and bitamoprost free acid with an amino acid selected from the group consisting of arginine, homoarginine, N(delta)-methyl-L-arginine, L-canavanine, D-canavanine, DL-canavanine, L-\(\alpha\)-amino-\(\beta\)-guanidinopropionic acid, \(\gamma\)-guanidinobutyric acid, and citrulene to form a salt;

neutralizing the salt to recover the prostaglandin free acid; and

converting the prostaglandin free acid to a prostaglandin analog.

51. The method of claim 14, wherein the prostaglandin analog is an ester.

52. The method of claim 14, wherein the prostaglandin analog is an amide.
53. The method of claim 14, wherein the prostaglandin analog binds to the prostaglandin F receptor.

54. A method of making a prostaglandin comprising

reacting a prostaglandin free acid selected from the group consisting of latanoprost free acid, travoprost free acid, fluoprostol free acid, tafluprost free acid, and bitamoprost free acid with an amino acid selected from the group consisting of arginine, homoarginine, N(delta)-methyl-L-arginine, L-canavanine, D-canavanine, DL-canavanine, L-α-amino-β-guanidinopropionic acid, γ-guanidinobutyric acid, and citrulene to form a salt; and

converting the salt to a prostaglandin.

55. The method of claim 18, wherein the prostaglandin binds to the prostaglandin F receptor.

56. A method of treating glaucoma, or other eye disease comprising administering to a subject in need thereof an effective amount of a salt according to claim 1.

57. A method of improving nasal patency or treating neurogenic bladder comprising administering to a subject in need thereof an effective amount of a salt according to claim 1.

58. A method of treating osteoporosis comprising administering to a subject in need thereof an effective amount of a salt according to claim 1.

59. A method of treating skin disorders, respiratory disorders, circulatory disorders, gastrointestinal disorders, hair loss or fertility control comprising administering to a subject in need thereof an effective amount of a salt according to claim 1.

60. A method of reducing ocular pressure comprising contacting a cell with an amount of a salt according to claim 1 effective to reduce ocular pressure.

61. The method of claim 24, wherein the cell is in a subject.
FIG. 6
FIG. 9