ABSTRACT

A method for treating hair loss in mammals uses compositions containing 2-decarboxy-2-phosphino prostaglandin derivatives. The compositions can be applied topically to the skin. The compositions can arrest hair loss, reverse hair loss, and promote hair growth. Compositions containing 2-decarboxy-2-phosphino prostaglandin derivatives can also be used to lower intraocular pressure and treat bone disorders.
COSMETIC AND PHARMACEUTICAL COMPOSITIONS AND METHODS USING 2-DECARBOXY-2-PHOSPHINICO DERIVATIVES

FIELD OF THE INVENTION

This invention relates to compositions and methods for using 2-decarboxy-2-phosphinico derivatives of prostaglandins. More particularly, this invention relates to the use of 2-decarboxy-2-phosphinico derivatives of prostaglandins for treating hair loss in mammals. This invention further relates to the use of 2-decarboxy-2-phosphinico derivatives of prostaglandins for lowering intraocular pressure and treating bone disorders in mammals.

BACKGROUND OF THE INVENTION

Hair Loss—Cosmetic Treatment

Hair loss is a common problem which is, for example, naturally occurring or chemically promoted through the use of certain therapeutic drugs designed to alleviate conditions such as cancer. Often such hair loss is accompanied by lack of hair re-growth which causes partial or full baldness.

Hair growth on the scalp does not occur continuously, but rather occurs by a cycle of activity involving alternating periods of growth and rest. This cycle is divided into three main stages: anagen, catagen, and telogen. Anagen is the growth phase of the cycle and is characterized by penetration of the hair follicle deep into the dermis with rapid proliferation of cells which are differentiating to form hair. The next phase is catagen, which is a transitional stage marked by the cessation of cell division, and during which the hair follicle regresses through the dermis and hair growth ceases. The next phase, telogen, is characterized as the resting stage during which the regressed follicle contains a germ with tightly packed dermal papilla cells. At telogen, the initiation of a new anagen phase is caused by rapid cell proliferation in the germ, expansion of the dermal papilla, and elaboration of basement membrane components. When hair growth ceases, most of the hair follicles reside in telogen and anagen is not engaged, thus causing the onset of full or partial baldness.

Attempts to invoke the re-growth of hair have been made by, for example, the promotion or prolongation of anagen. Currently, there are two drugs approved by the United States Food and Drug Administration for the treatment of male pattern baldness: topical minoxidil (marketed as ROGAINE® by Pharmacia & Upjohn), and oral finasteride (marketed as PROPECIA® by Merck & Co., Inc.). However, the search for efficacious hair growth inducers is ongoing due to factors including safety concerns and limited efficacy.

The thyroid hormone thyroxine ("T4") converts to triiodothyronine ("T3") in human skin by deiodinase I, a selenoprotein. Selenium deficiency causes a decrease in T3 levels due to a decrease in deiodinase I activity; this reduction in T3 levels is strongly associated with hair loss. Consistent with this observation, hair growth is a reported side effect of administration of T4. See, e.g., Herman, “Peripheral Effects of I- Thyroxine on Hair Growth and Coloring in Cattle”, Journal of Endocrinology, Vol. 20, pp. 282-292, (1960); and Gunaratnam, “The Effects of Thyroxine on Hair Growth in the Dog”, J. Small Anim. Pract., Vol. 27, pp. 17-29 (1986). Furthermore, T3 and T4 have been the subject of several patent publications relating to treatment of hair loss. See, e.g., Fischer et al., DE 1,617,477, published Jan. 8, 1970; Mortimer, GB 2,138,286, published Oct. 24, 1984; and Lindenbaum, WO 96/25943, assigned to Life Medical Sciences, Inc., published Aug. 29, 1996.

Unfortunately, however, administration of T3 or T4, or both, to treat hair loss is often not practicable because these thyroid hormones can induce significant cardiotoxicity. See, e.g., Walker et al., U.S. Pat. No. 5,284,971, assigned to Syntex, issued Feb. 8, 1994 and Emmett et al., U.S. Pat. No. 5,061,798, assigned to Smith Kline & French Laboratories, issued Oct. 29, 1991.

In an alternative approach, prostaglandins have been proposed to promote hair growth because prostaglandins may have a similar benefit to thyroid hormones, i.e., increasing hair length and changing pigmentation. Naturally occurring prostaglandins (e.g., PGA₂, PGB₂, PGE₁, PGF₂α, and PGL₂) are C-20 unsaturated fatty acids. PGF₂α, the naturally occurring Prostaglandin F analog in humans, is characterized by hydroxyl groups at the C9 and C11 positions on the alicyclic ring, a cis-double bond between C5 and C6, and a trans-double bond between C13 and C14. PGF₂α has the formula:

![Diagram of PGF₂α]


Prostaglandins in general have a wide range of biological activities. For example, PGE₂ has the following properties: a) regulator of cell proliferation, b) regulator of cytokine synthesis, c) regulator of immune responses and d) inducer of vasodilatation. Vasodilatation is thought to be one of the mechanisms of how minoxidil provides a hair growth benefit. In vitro results in the literature also indicate some anti-inflammatory properties of the prostaglandins. c.f.; Tanaka, H., Br J. Pharm., 116, 2298, (1995).
However, previous attempts at using prostaglandins to promote hair growth have been unsuccessful. Different prostaglandins can bind to multiple receptors at various concentrations with a biphasic effect. Therefore, it is an object of this invention to provide methods for using prostaglandins to grow hair and to provide compositions that promote hair growth. It is a further object of this invention to provide a selection of appropriate prostaglandins that will promote hair growth in humans and lower animals.

Bone Disorders—Pharmaceutical Treatment

In addition to the biological activities discussed above, prostaglandins are also known to affect bone. Therefore, it is a further object of this invention to provide compositions and methods for using prostaglandins to treat bone disorders.

Accelerated bone loss may result from drug administration, such as corticosteroids, prolonged bed rest, disuse of a limb, and microgravity. In osteoporotics, an imbalance in the bone remodeling process develops in which bone is resorbed at a rate faster than it is being made. Although this imbalance occurs to some extent in most individuals, male and female, as they age, it is more severe and occurs at a younger age in osteoporotics, particularly those who develop the post menopausal form of the condition. Bone loss due to the above conditions can result in complete removal of trabeculae and a deterioration of bone architecture such that the strength of the remaining bone decreases disproportionately.

To completely return the bone to normal strength, new trabeculae should be formed to restore architecture and increase bone mass. When restoration of normal architecture is associated with an increase in strength and return to normal stiffness and shock absorbing capability, the bone is less likely to fracture. Subjects suffering from other bone disorders, such as osteoarthritis, Paget’s disease, periodontal disease, and fractures may also benefit from treatments that restore normal architecture and bone mass.

Various agents have been tried in attempts to treat bone disorders by slowing bone loss or increasing bone mass. Agents for slowing bone loss and reestablishing bone density are exemplified by antiresorptive agents such as bisphosphonates.

Prostaglandin E analogs are potent stimulators of bone resorption and formation. Anabolic agents such as some prostaglandin E analogs may be detrimental to one suffering from bone disorders such as osteoporosis because increased resorption may cause perforation and loss of trabeculae or may weaken the existing trabecular structure. Increased resorption may also occur in cortical bone, which may increase the incidence of fracture at some sites.

Anabolic agents such as fluoride and other prostaglandin E analogs have been used to increase bone mass. However, such agents have failed to build bone that is structurally and architecturally similar to the type of bone lost.

Naturally occurring PGE₂, shown above, is also known to affect bone resorption. However, naturally occurring prostaglandins have several drawbacks that limit their desirability for systemic administration. Naturally occurring prostaglandins are characterized by their activity at a certain prostaglandin receptor, however, their activity is not limited to any one receptor. Therefore, systemic administration of naturally occurring prostaglandins can cause side effects such as inflammation, surface irritation, smooth muscle contraction, pain, and bronchoconstriction.

Therefore, it is an object of this invention to provide compositions and methods using prostaglandins to treat bone disorders without significant undesirable side effects. It is a further object of this invention to provide a selection of appropriate prostaglandins that will promote bone growth in humans and lower animals.

Intraocular Pressure—Pharmaceutical Treatment

In addition to the pharmacological properties discussed above, naturally occurring prostaglandins are also known to reduce intraocular pressure. Reduction of intraocular pressure is effective to treat disorders such as glaucoma. See C. Iljibris, G. Selen, B. Resul, J. Sernschantz, and U. Hacksell, “Derivatives of 17-Phenyl-18, 19,20-trinorprostaglandin F₂–. Isopropyl Ester: Potential Antiglaucoma Agents”, Journal of Medicinal Chemistry, Vol. 38, No. 2, pp. 289-304 (1995). However, as discussed above, the naturally occurring prostaglandins generally are not specific for any one prostaglandin receptor, and thus are known to cause side effects.

Therefore, it is an object of this invention to provide compositions and methods using prostaglandins to lower intraocular pressure without significant undesirable side effects. It is a further object of this invention to provide a selection of appropriate prostaglandins that will lower intraocular pressure in humans and lower animals.

SUMMARY OF THE INVENTION

This invention relates to compositions and methods for treating hair loss. The methods comprise administering the compositions comprising specific prostaglandins that interact strongly with hair-selective receptors, such as the FP receptor. The choice of prostaglandin is important because the prostaglandin must selectively activate the FP receptor and not activate any other receptors that would negate the effect of activating the FP receptor or that would cause significant undesirable side effects. The prostaglandins used in this invention are 2-decarboxy-2-phosphino derivatives of prostaglandins. This invention further relates to the use of 2-decarboxy-2-phosphino derivatives of prostaglandins to prepare compositions for treating hair loss. The compositions comprise: component A) the 2-decarboxy-2-phosphino derivative of a prostaglandin, component B) a carrier, and optionally component C) an activity enhancer.

This invention further relates to compositions and methods for lowering intraocular pressure. The methods comprise administering, to subjects suffering from conditions such as glaucoma, compositions comprising 2-decar-
boxy-2-phosphinico derivatives of prostaglandins. This invention further relates to the use of 2-decarboxy-2-phosphinico derivatives of prostaglandins to prepare compositions for lowering intracranial pressure.

**DETAILED DESCRIPTION OF THE INVENTION**

**[0024]** In one aspect, this invention relates to compositions for treating hair loss in mammals. “Treating hair loss” includes arresting hair loss or reversing hair loss, or both, and promoting hair growth.

**[0025]** Publications and patents are referred to throughout this disclosure. All U.S. Patents cited herein are hereby incorporated by reference.

**[0026]** All percentages, ratios, and proportions used herein are by weight unless otherwise specified.

**Definition and Usage of Terms**

**[0027]** The following is a list of definitions for terms, as used herein:

**[0028]** “Activate” means binding and signal transduction of a receptor.

**[0029]** “Acy1 group” means a monovalent group suitable for acylating a nitrogen atom to form an amide or carbamate, an alcohol to form a carbonate, or an oxygen atom to form an ester group. Preferred acyl groups include benzoyl, acetyl, tert-butyl acetyl, para-phenyl benzoyl, and trifluoro-acetyl. More preferred acyl groups include acetyl and benzoyl. The most preferred acyl group is acetyl.

**[0030]** “Aromatic group” means a monovalent group having a monocyclic ring structure or fused bicyclic ring structure. Monocyclic aromatic groups contain 5 to 10 carbon atoms, preferably 5 to 7 carbon atoms, and more preferably 5 to 6 carbon atoms in the ring. Bicyclic aromatic groups contain 8 to 12 carbon atoms, preferably 9 or 10 carbon atoms in the ring. Aromatic groups are unsubstituted. The most preferred aromatic group is phenyl.

**[0031]** “Carbocyclic group” means a monovalent saturated or unsaturated hydrocarbon ring. Carbocyclic groups are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic carbocyclic groups contain 4 to 10 carbon atoms, preferably 4 to 7 carbon atoms, and more preferably 5 to 6 carbon atoms in the ring. Bicyclic carbocyclic groups contain 8 to 12 carbon atoms, preferably 9 to 10 carbon atoms in the ring. Carbocyclic groups are unsubstituted. Preferred carbocyclic groups include cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. More preferred carbocyclic groups include cyclohexyl, cycloheptyl, and cyclooctyl. The most preferred carbocyclic group is cyclohexyl. Carbocyclic groups are not aromatic.

**[0032]** “Cyan0 group” means a group containing a nitrile functionality.

**[0033]** “FP agonist” means a compound that activates the FP receptor.

**[0034]** “FP receptor” means known human FP receptors, their splice variants, and undescribed receptors that have similar binding and activation profiles as the known human FP receptors. “FP” means the receptor is of the class which has the highest affinity for PGF$_{2\alpha}$ of all the naturally occurring prostaglandins. FP refers to a known protein.

**[0035]** “Halogen atom” means F, Cl, Br, or I. Preferably, the halogen atom is F, Cl, or Br; more preferably Cl or F; and most preferably F.

**[0036]** “Halogenated heterogenous group” means a substituted heterogenous group or a substituted heterocyclic group, wherein at least one substituent is a halogen atom. Halogenated heterogenous groups can have a straight, branched, or cyclic structure. Preferred halogenated heterogenous groups have 1 to 12 carbon atoms, more preferably 1 to 6 carbon atoms, and most preferably 1 to 3 carbon atoms. Preferred halogen atom substituents are Cl and F.

**[0037]** “Halogenated hydrocarbon group” means a substituted monovalent hydrocarbon group or a substituted carbocyclic group, wherein at least one substituent is a halogen atom. Halogenated hydrocarbon groups can have a straight, branched, or cyclic structure. Preferred halogenated hydrocarbon groups have 1 to 12 carbon atoms, more preferably 1 to 6 carbon atoms, and most preferably 1 to 5 carbon atoms. Preferred halogen atom substituents are Cl and F. The most preferred halogenated hydrocarbon group is trifuoroethyl.

**[0038]** “Heteroaromatic group” means an aromatic ring containing carbon and 1 to 4 heteroatoms in the ring. Heterocyclic groups are monocyclic or fused bicyclic rings. Monocyclic heteroaromatic groups contain 5 to 10 member atoms (i.e., carbon and heteroatoms), preferably 5 to 7, and more preferably 5 to 6 in the ring. Bicyclic heteroaromatic rings contain 8 to 12 member atoms, preferably 9 or 10 in the ring. Heteroaromatic groups are unsubstituted. Preferred heteroaromatic groups include thienyl, thiazolyl, purinyl, pyrimidyl, pyridyl, and furanyl. More preferred heteroaromatic groups include thienyl, furanyl, and pyridyl. The most preferred heteroaromatic group is thienyl.

**[0039]** “Heteroatom” means an atom other than carbon in the ring of a heterocyclic group or the chain of a heterogenous group. Preferably, heteroatoms are selected from the group consisting of nitrogen, sulfur, and oxygen atoms. Groups containing more than one heteroatom may contain different heteroatoms. “Heterocyclic group” means a saturated or unsaturated ring structure containing carbon and 1 to 4 heteroatoms in the ring. No two heteroatoms are adjacent in the ring. Heterocyclic groups are not aromatic. Heterocyclic groups are monocyclic, or are fused or bridged bicyclic ring systems. Monocyclic heterocyclic groups contain 4 to 10 member atoms (i.e., including both carbon atoms and at least 1 heteroatom), preferably 4 to 7, and more preferably 5 to 6 in the ring. Bicyclic heterocyclic groups contain 8 to 12 member atoms, preferably 9 or 10 in the ring. Heterocyclic groups are unsubstituted. Preferred heterocyclic groups include piperazyl, morpholinyl, tetrahydrofuranyl, tetrahydropranonyl, and piperidyl.

**[0040]** “Heterogeneous group” means a saturated or unsaturated chain containing 1 to 18 member atoms (i.e., including both carbon and at least one heteroatom). No two heteroatoms are adjacent. Preferably, the chain contains 1 to 12 member atoms, more preferably 1 to 6, and most preferably 1 to 4. The chain may be straight or branched. Preferred branched heterogeneous groups have one or two
branches, preferably one branch. Preferred heterogeneous groups are saturated. Unsaturated heterogeneous groups have one or more double bonds, one or more triple bonds, or both. Preferred unsaturated heterogeneous groups have one or two double bonds or one triple bond. More preferably, the unsaturated heterogeneous group has one double bond. Heterogeneous groups are unsubstituted.

“Monovalent hydrocarbon group” means a chain of 1 to 18 carbon atoms, preferably 1 to 12 carbon atoms. “Lower monovalent hydrocarbon group” means a monovalent hydrocarbon group having 1 to 6, preferably 1 to 4 carbon atoms. Monovalent hydrocarbon groups may have a straight chain or branched chain structure. Preferred monovalent hydrocarbon groups have one or two branches, preferably 1 branch. Preferred monovalent hydrocarbon groups are saturated. Unsaturated monovalent hydrocarbon groups have one or more double bonds, one or more triple bonds, or combinations thereof. Preferred unsaturated monovalent hydrocarbon groups have one or two double bonds or one triple bond; more preferred unsaturated monovalent hydrocarbon groups have one double bond.

“Pharmacologically acceptable” means suitable for use in a human or other mammal.

“Prostaglandin” means a fatty acid derivative which has a variety of potent biological activities of a hormonal or regulatory nature.

“Protecting group” is a group that replaces the active hydrogen of a hydroxyl moiety thus preventing undesired side reaction at the hydroxyl moiety. Use of protecting groups in organic synthesis is well known in the art. Examples of protecting groups are found in Chapter 2 Protecting Groups in Organic Synthesis by Greene, T. W. and Wuts, P. G. M., 2nd ed., Wiley & Sons, Inc., 1991. Preferred protecting groups include silyl ethers, alkoxymethyl ethers, tetrahydropropylamyl, tetrahydrofuranyl, esters, and substituted or unsubstituted benzyl ethers.

“Safe and effective amount” means a quantity of a prostaglandin high enough to provide a significant positive modification of the subject’s condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio).

“Selective” means having a binding or activation preference for a specific receptor over other receptors which can be quantitated based upon receptor binding or activation assays.

“Subject” means a living vertebrate animal such as a mammal (preferably human) in need of treatment.

“Substituted aromatic group” means an aromatic group wherein 1 to 4 of the hydrogen atoms bonded to carbon atoms in the ring have been replaced with other substituents. Preferred substituents include: halogen atoms, cyano groups, monovalent hydrocarbon groups, substituted monovalent hydrocarbon groups, heterocyclic groups, aromatic groups, substituted aromatic groups, or any combination thereof. More preferred substituents include halogen atoms, monovalent hydrocarbon groups, substituted monovalent hydrocarbon groups, naphthyl, substituted aromatic groups, or any combination thereof. More preferred substituents include halogen atoms and substituted monovalent hydrocarbon groups. Substituted aromatic group does not include aromatic rings.

“Substituted carbocyclic group” means a carbocyclic group wherein 1 to 4 hydrogen atoms bonded to carbon atoms in the ring have been replaced with other substituents. Preferred substituents include: halogen atoms, cyano groups, monovalent hydrocarbon groups, substituted monovalent hydrocarbon groups, aromatic groups, substituted aromatic groups, or any combination thereof. More preferred substituents include halogen atoms and substituted monovalent hydrocarbon groups. Carbocyclic group does not include aromatic rings.

“Substituted heteroaromatic group” means a heteroaromatic group wherein 1 to 4 hydrogen atoms bonded to carbon atoms in the ring have been replaced with other substituents. Preferred substituents include: halogen atoms, cyano groups, monovalent hydrocarbon groups, substituted monovalent hydrocarbon groups, heterocyclic groups, substituted heterocyclic groups, phenyl groups, phenoxy groups, or any combination thereof. More preferred substituents include halogen atoms, halogenated hydrocarbon groups, hydrogenated heterocyclic groups, monovalent hydrocarbon groups, and phenyl groups.

“Substituted heterocyclic group” means a heterocyclic group wherein 1 to 4 hydrogen atoms bonded to carbon atoms in the ring have been replaced with other substituents. Preferred substituents include: halogen atoms, cyano groups, monovalent hydrocarbon groups, substituted monovalent hydrocarbon groups, heterocyclic groups, substituted heterocyclic groups, halogenated hydrocarbon groups, hydrogenated heterocyclic groups, phenyl groups, phenoxy groups, or any combination thereof. More preferred substituents include halogen atoms and halogenated hydrocarbon groups. Substituted heterocyclic groups are not aromatic.

“Substituted heterogeneous group” means a heterogeneous group wherein 1 to 4 of the hydrogen atoms bonded to carbon atoms in the chain have been replaced with other substituents. Preferred substituents include halogen atoms, hydroxy groups, alkoxy groups (e.g., methoxy, ethoxy, propoxy, butoxy, and pentoxy), aryloxy groups (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenyl, benzyl, alkoxybenzylphenoxyl, and acyloxyphenoxyl), acyloxy groups (e.g., propionyloxy, benzoyl, and acetoxy), carboxamoyloxy groups, carboxy groups, mercapto groups, alkythio groups, acylthio groups, arythio groups (e.g., phenylthio, chlorophenylthio, alkylyphenylthio, alkoxyphenylthio, benzylthio, and alkoxybenzylphenylthio), aromatic groups (e.g., phenyl and tolyl), substituted aromatic groups (e.g., alkoxyphenyl, alkoxybenzyl, and alkoxybenzylphenyl), alkoxybenzyl, alkylamido groups of 1 to 3 carbon atoms, carbamamido, ureido, and guanidino).

“Substituted monovalent hydrocarbon group” means a monovalent hydrocarbon group wherein 1 to 4 of the hydrogen atoms bonded to carbon atoms in the ring have been replaced with other substituents. Preferred substituents include halogen atoms; halogenated hydrocarbon groups; halogenated heterocyclic groups; alkyl groups
(e.g., methyl, ethyl, propyl, and butyl); hydroxy groups; alkoxo groups (e.g., methoxy, ethoxy, propoxy, butoxy, and pentoxy); aryloxy groups (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxo, benzylxoy, alkoxycarbon- 
ylphenoxy, and aclyloxyphenoxy); aclyoxy groups (e.g., pro- 
pionylxoy, benzoyloxy, and acetoxo); carbamoyloxy groups; 
carboxy groups; mercapto groups; alkylthio groups; aclythio 
groups; ary1thio groups (e.g., phenylthio, chlorophenylthio, 
alkylphynithio, alkoxycarboxylxthio, and halophenylithio); het-
recyclicl groups; heteroaryl groups; and amino groups (e.g., 
arnino, mon6- and di-alkylamino groups of 1 to 3 carbon 
atoms, methylphenylamino, methylbenzylamino, alkanylam-
imo groups of 1 to 3 carbon atoms, carbamamido, urido, 
and guanidino).

Prostaglandins Used in the Invention

[0054] The prostaglandins suitable for use in this invention 
are selected from the group consisting of 2-decarboxy-
2-phosphino derivatives of prostaglandins; optical isom-
ers, diastereomers, and enantiomers of the 2-decarboxy-
2-phosphino derivatives; pharmaceutically-acceptable 
 salts of the 2-decarboxy-2-phosphino derivatives; and bio-
 hydrolyzable amidcs, esters, and imides of the 2-decarboxy-
2-phosphino derivatives.

[0055] Suitable 2-decarboxy-2-phosphino derivatives 
can have a formula selected from the group consisting of:

![Formula I](image)

![Formula II](image)

![Formula III](image)

[0056] R is selected from the group consisting of a 
hydrogen atom, lower monovalent hydrocarbon groups, 
lower substituted monovalent hydrocarbon groups, 
and lower heterogeneous groups. R is preferably selected 
from the group consisting of a hydrogen atom; an alkyl group 
such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 
and t-butyl; a halogenated hydrocarbon group such as trif-
luoromethyl or CH3CH2CF3; CH3CH2OH, and 
CH3CH2CH2OH. More preferably, R is a hydrogen atom, 
methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, 
trifluoromethyl, CH3CH2CF3, CH3CH2OH, or 
CH3CH2CH2OH. Most preferably, R is a hydrogen atom, 
methyl, ethyl, n-propyl, isopropyl, or CH3CH2OH.

[0057] R is selected from the group consisting of a 
hydrogen atom, a monovalent hydrocarbon group, a substi-
tuted monovalent hydrocarbon group, a heterogeneous 
group, a substituted heterogeneous group, a carbocyclic 
group, a substituted carbocyclic group, a heterocyclic group, 
a substituted heterocyclic group, an aromatic group, a substi-
tuted aromatic group, a heteroaromatic group, and a 
substituted heteroaromatic group. Preferably R is 
H, CH3CO2H, CH2(O)NH2OH, methyl, CF3, ethyl, n-propyl, 
isopropyl, CH3CH2OH, CH3CH(OH)CH2OH, benzyl, or 
t-butyl. More preferably, R is H, methyl, CF3, ethyl, n-pro-
pyl, isopropyl, CH3CH2OH, CH3CH(OH)NH2OH, and benzyl.

[0058] R is selected from the group consisting of an 
hydrogen atom, a sulfur atom, and NH. Preferably, R is an 
oxygen atom or NH; more preferably, R is an oxygen atom.

[0059] R is selected from the group consisting of an 
hydrogen atom and a sulfur atom. Preferably, R is an 
oxygen atom.

[0060] R is a divalent group. R is selected from the group 
consisting of a hydrocarbon group, a substituted hydro-
carbon group, a hetereogeneous group, and a substituted het-
erogeneous group. R may be saturated or unsaturated, i.e., R 
may contain one or more single bond, double bond, triple 
bond, or combinations thereof. When R is a hetereogeneous 
group, R5 has only one heteroatom, which is selected from 
the group consisting of oxygen, sulfur, and nitrogen. The 
preferred heteroatom is oxygen. R preferably has 1 to 5 
member atoms, more preferably 3 to 5 member atoms.

[0061] Bond a is selected from the group consisting of a 
single bond, a trans double bond, and a triple bond.

[0062] R is a divalent group selected from the group 
consisting of C(O) and (R)(OR).

[0063] R is selected from the group consisting of a 
divalent group having the formula (CR(R))N, where 
R is an integer from 0 to 3, and q is an integer 
from 0 to 3, and wherein X is a selected from the group 
consisting of an oxygen atom, a divalent hydrocarbon group, 
a sulfur atom, SO2, SO3, and NR. Preferably, X is selected 
from the group consisting of a single bond, a trans double 
 bond, a triple bond, an oxygen atom, a sulfur atom, and 
NR.

[0064] R is selected from the group consisting of a methyl 
group, a carbocyclic group, a substituted carbocyclic group, a 
heterocyclic group, a substituted heterocyclic group, an 
amic group, a substituted amic group, a heteroaromatic group, 
a substituted heteroaromatic group. When R is a 
monocyclic group, it has 5 to 10 member atoms. When R is 
a bicyclic group, it has 8 to 12 member atoms. Preferably,
R\(^8\) is selected from the group consisting of a monocyclic carbocyclic group, a substituted monocyclic carbocyclic group, a monocyclic heterocyclic group, a substituted monocyclic heterocyclic group, aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group.

[0065] R\(^9\) is a hydrogen atom or a lower monovalent hydrocarbon group. Preferably, R\(^9\) is a hydrogen atom.

[0066] R\(^10\) is a hydrogen atom or a lower monovalent hydrocarbon group. Preferably, R\(^10\) is a hydrogen atom.

[0067] Component A) may also be any optical isomer, diastereomer, and enantiomer of any of the above structures; or any pharmaceutically-acceptable salts of any of the above structures; or any biohydrolyzable amides, esters, and imides of any of the above structures; or combinations thereof.

[0068] The prostaglandin used in this invention preferably has the formula:

\[
\text{He CIP(OR) RP(OR)}
\]

1) Optionally reduce bond a
2) Remove protecting groups
8 re O R toluene, heat

[0069] wherein, R\(_1\), R\(_2\), R\(_3\), R\(_4\), R\(_5\), R\(_6\), R\(_7\), R\(_8\), and bond a are as described above. More preferably, R\(_9\) is a hydrogen atom.

[0070] Suitable prostaglandins for component A) can be prepared by conventional organic syntheses. Examples of suitable prostaglandins for component A) can be prepared by the following reaction scheme.
[0071] In the reaction scheme above, R¹, R², R³, R⁴, R⁵, R⁶, and bond a are as described above, X is a halogen atom, and Q and Q² are protecting groups. The Corey Lactone (S1a) starting material is commercially available (from Aldrich Chemical Company or Cayman Chemical Company). Known Wadsworth-Horner-Emmons chemistry is used to attach the bottom chain of the desired prostaglandin to the Corey Lactone, creating compounds of the type S1b. There follows standard prostaglandin omega chain manipulation and functional group protection, including optional alkene reduction, which creates compounds of type S1c. At this point, the standard course of prostaglandin synthesis is altered; the omega-functionalized Wittig reagent depicted is used to create 2-decarboxy prostaglandin derivatives of the type S1d. When the carboxycyclic acid containing prostaglandin is available, compounds of the type S1d are also obtained by a one-carbon degradation using a modification of the Hunsdiecker reaction.

[0072] Compounds depicted by S1e are available from compounds of the type S1d via a phosphinite coupling reaction with an allyl diethyloxyphosphinite, which is obtained, as shown, from the chlorodiethyloxyphosphine reagent, which is commercially available. Compounds depicted by Formula III are available from compounds of the type S1e via optional removal of the alkene and subsequent removal of the protecting groups Q and Q² of S1e.

[0073] Alternatively, compounds of the type S1f can be prepared from intermediate S1e, where the protecting groups Q and Q² are judiciously selected from a variety available to those skilled in the art (see, for example: *Protecting Groups in Organic Synthesis* by Greene, T. W. and Wuts, P. G. M., 2nd ed., Wiley & Sons, Inc., 1991). Subsequent removal of Q at C11, followed by oxidation would give the ketone precursor to S1f. Compounds of the type S1f can then be obtained by final deprotection.

[0074] Compounds of Formula I can be prepared from compounds of formula S1f by condensation with hydroxyl amine. Compounds of Formula II can be reduced to prepare compounds of Formula I by treatment with sodium cyanoborohydride in THF:acetic acid (1:1) and thereafter quenching with HCl. Using conventional organic synthesis techniques, one skilled in the art could prepare prostaglandins suitable for use in this invention.

[0075] Examples of suitable prostaglandins of Formula I include Formula 1A. Formula 1A is
TABLE 1A

Substituents in Formula 1A

<table>
<thead>
<tr>
<th>R²</th>
<th>R¹</th>
<th>R⁷</th>
<th>R⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>CH₃</td>
<td>CH₂S</td>
<td></td>
</tr>
<tr>
<td>H</td>
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<td>CH₂S</td>
<td></td>
</tr>
<tr>
<td>H</td>
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</tr>
</tbody>
</table>

wherein R¹, R⁷, R⁸, and R⁹, are defined in Table 1A.
TABLE 1A-continued

Substituents in Formula 1A

wherein R¹, R⁷, R⁸, and R⁹, are defined in Table 1A.

<table>
<thead>
<tr>
<th>R⁷</th>
<th>R¹</th>
<th>R⁸</th>
<th>R⁹</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>CH₃</td>
<td>CH₂CH₃</td>
<td></td>
</tr>
</tbody>
</table>

Examples of suitable prostaglandins of Formula II include Formula 2A. Formula 2A is

TABLE 2A-continued

Substituents in Formula 2A

wherein a, b, R¹, and R⁷–R⁹ are defined in Table 2A.

<table>
<thead>
<tr>
<th>b</th>
<th>a</th>
<th>R¹</th>
<th>R⁷–R⁹</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis</td>
<td>trans</td>
<td>CH₃</td>
<td></td>
</tr>
<tr>
<td>single</td>
<td>single</td>
<td>CH₃</td>
<td></td>
</tr>
<tr>
<td>single</td>
<td>single</td>
<td>CH₂CH₃</td>
<td></td>
</tr>
</tbody>
</table>

Examples of suitable prostaglandins of Formula III include Formulas 3A and 3B. Formula 3A is
### TABLE 3A

Substituents in Formula 3A

<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^7$</th>
<th>$R^8$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{CH}_2\text{CH}_2$</td>
<td><img src="image1.png" alt="Image of substituent" /></td>
</tr>
<tr>
<td>$\text{CH}_2$</td>
<td>$\text{CH}_2\text{S}$</td>
<td><img src="image2.png" alt="Image of substituent" /></td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{CH}_2\text{O}$</td>
<td><img src="image3.png" alt="Image of substituent" /></td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_3$</td>
<td>$\text{CH}_2\text{O}$</td>
<td><img src="image4.png" alt="Image of substituent" /></td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_3$</td>
<td>$\text{CH}_2\text{O}$</td>
<td><img src="image5.png" alt="Image of substituent" /></td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_3\text{CH}_3$</td>
<td>$\text{CH}_2\text{O}$</td>
<td><img src="image6.png" alt="Image of substituent" /></td>
</tr>
<tr>
<td>$\text{CH}$</td>
<td>$\text{CH}_2\text{NH}$</td>
<td><img src="image7.png" alt="Image of substituent" /></td>
</tr>
</tbody>
</table>

wherein $R^1$, $R^7$, and $R^8$ are defined in Table 3A.

### TABLE 3A-continued

Substituents in Formula 3A

<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^7$</th>
<th>$R^8$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{CH}_2$</td>
<td><img src="image8.png" alt="Image of substituent" /></td>
</tr>
<tr>
<td>$\text{CH}_2\text{CH}$</td>
<td>$\text{CH}_2\text{O}$</td>
<td><img src="image9.png" alt="Image of substituent" /></td>
</tr>
<tr>
<td>$\text{CH}_2\text{CH}$</td>
<td>$\text{CH}_2\text{O}$</td>
<td><img src="image10.png" alt="Image of substituent" /></td>
</tr>
<tr>
<td>$\text{CH}_2\text{NH}$</td>
<td>$\text{CH}_2\text{O}$</td>
<td><img src="image11.png" alt="Image of substituent" /></td>
</tr>
</tbody>
</table>
TABLE 3B-continued

Compositions of the Invention

Hair Loss

[0079] This invention further relates to a composition for treating hair loss. "Treating hair loss" means arresting hair loss, reversing hair loss, or both, and promoting hair growth. The composition comprises A) the PGF described above and B) a carrier. The composition may further comprise C) one or more optional activity enhancers.

[0080] The composition can be a pharmaceutical or cosmetic composition, administered for treatment or prophylaxis of hair loss. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington’s Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa. (1990).

[0081] The composition further comprises component B) a carrier. "Carrier" means one or more compatible substances that are suitable for administration to a mammal. Carrier includes solid or liquid diluents, hydrotopes, surface-active agents, and encapsulating substances. "Compatible" means that the components of the composition are capable of being commingled with the prostaglandins, and with each other, in a manner such that there is no interaction which would substantially reduce the efficacy of the composition under ordinary use situations. Carriers must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the mammal being treated. The carrier can be inert, or it can possess pharma-
ceutical benefits, cosmetic benefits, or both, depending on the intended use as described herein.

[0082] The choice of carrier for component B) depends on the route by which A) the prostaglandin will be administered and the form of the composition. The composition may be in a variety of forms, suitable, for example, for systemic administration (e.g., oral, rectal, nasal, sublingual, buccal, or parenteral) or topical administration (e.g., local application on the skin, ocular, liposome delivery systems, or iontophoresis). Topical administration directly to the locus of desired hair growth is preferred.

[0083] Carriers for systemic administration typically comprise one or more ingredients selected from the group consisting 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) surfactants, combinations thereof, and others.

[0084] Ingredient a) is a diluent. Suitable diluents include sugars such as glucose, lactose, dextrose, and sucrose; polyols such as propylene glycol; calcium carbonate; sodium carbonate; glycérin; mannitol; sorbitol; and maltodextrin.

[0085] Ingredient b) is a lubricant. Suitable lubricants are exemplified by solid lubricants including silica, talc, stearic acid and its magnesium salts and calcium salts, calcium sulfate; and liquid lubricants such as propylene glycol and vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma.

[0086] Ingredient c) is a binder. Suitable binders include polyvinylpyrrolidone; magnesium aluminum silicate; starches such as corn starch and potato starch; gelatin; tragacanth; and cellulose and its derivatives, such as sodium carboxymethylcellulose, ethylcellulose, methylcellulose, microcrystalline cellulose, and hydroxypropylcellulose; carborner; providone; acacia; guar gum; and xanthan gum.

[0087] Ingredient d) is a disintegrant. Suitable disintegrants include agar, alginic acid and the sodium salt thereof, effervescent mixtures, crosscarmellose, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, clays, and ion exchange resins.

[0088] Ingredient e) is a colorant such as an FD&C dye.

[0089] Ingredient f) is a flavor such as menthol, peppermint, and fruit flavors.

[0090] Ingredient g) is a sweetener such as saccharin and aspartame.

[0091] Ingredient h) is an antioxidant such as butylated hydroxyanisole, butylated hydroxytoluene, and vitamin E.

[0092] Ingredient j) is a preservative such as phenol, alky esters of para-hydroxybenzoic acid, benzoic acid and the salts thereof, boric acid and the salts thereof, sorbic acid and the salts thereof, chorbutanol, benzy alcohol, thimerosal, phe nylmercuric acetate and nitrate, nitromersol, benzalkonium chloride, cetlypyridinium chloride, methyl paraben, and propyl paraben. Particularly preferred are the salts of benzoic acid, cetlypyridinium chloride, methyl paraben and propyl paraben, and sodium benzoate.

[0093] Ingredient k) is a glidant such as silicon dioxide.

[0094] Ingredient m) is a solvent, such as water, isotonic saline, ethyl oleate, alcohols such as ethanol, glycérin, glycols (e.g., polypropylene glycol and polyethylene gly col), and buffer solutions (e.g., phosphate, potassium acetate, boric carborn, phosphoric, succinic, malic, tartaric, citric, acetic, benzoic, lactic, glycercine, gluconic, glutaric, and glutamic).

[0095] Ingredient n) is a suspending agent. Suitable suspending agents include AVICEL® RC-591 from FMC Corporation of Philadelphia, Pennsylvania and sodium alginate.

[0096] Ingredient o) is a surfactant such as lecithin, polysorbate 80, sodium lauryl sulfate, polyoxyethylene sor bitan fatty acid esters, polyoxyethylene monoalkyl ethers, sucrose monoesters, lanolin esters, and lanolin ethers. Suitable surfactants are known in the art and commercially available, e.g., the TWEEN®80 from Atlas Powder Company of Wilmington, Del.

[0097] Compositions for parenteral administration typically comprise A) 0.1 to 10% of a prostaglandin and B) 90 to 99.9% of a carrier comprising a) a diluent and m) a solvent. Preferably, component a) is propylene glycol and m) is ethanol or ethyl oleate.

[0098] 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 5%, and preferably from 25% to 50%, of A) the prostaglandin. The oral dosage compositions further comprise B) 50 to 95% of a carrier, preferably 50 to 75%.

[0099] Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed. Tablets typically comprise A) the prostaglandin, and 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. Preferred diluents include calcium carbonate, sodium carbonate, mannitol, lactose, and sucrose. Preferred binders include starch, and gelatin. Preferred disintegrants include alginic acid, and crosscarmellose. Preferred lubricants include magnesium stearate, stearic acid, and talc. Preferred 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, and fruit flavors.

[0100] Capsules (including time release and sustained release formulations) typically comprise A) the prostaglandin, and B) a carrier comprising one or more a) diluents disclosed above in a capsule comprising gelatin. Granules typically comprise A) the prostaglandin, and preferably further comprise k) glidants such as silicon dioxide to improve flow characteristics.

[0101] 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 can optimize appropriate ingredients without undue experimentation.

[0102] The solid compositions may also be coated by conventional methods, typically with pH or time-dependent
coatings, such that A) the prostaglandin is released in the gastrointestinal tract at various times to extend the desired action. The coatings typically comprise one or more components selected from the group consisting of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, acrylic resins such as EUDRAGIT® coatings (available from Rohm & Haas G.M.B.H. of Darmstadt, Germany), waxes, shellac, polyvinylpyrrolidone, and other commercially available film-coating preparations such as Dri-Klear, manufactured by Crompton & Knowles Corp., Mahwah, N.J. or OPADRY® manufactured by Colorcon, Inc., of West Point, Pa.

[0103] 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 A) the prostaglandin and B) a carrier comprising ingredients selected from the group consisting of a) diluents, c) colorants, and 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.

[0104] Other compositions useful for attaining systemic delivery of the subject compounds 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, carboxymethylcellulose, and hydroxypropylmethylcellulose. Such compositions may further comprise b) lubricants, c) colorants, f) flavors, g) sweeteners, h) antioxidants, and k) glidants.

[0105] The compositions for treating hair loss may further comprise component C) an optional activity enhancer. Component C) is preferably selected from the group consisting of i) hair growth stimulants (other than the prostaglandin) and ii) penetration enhancers.

[0106] Component i) is an optional hair growth stimulant. Component i) is exemplified by vasodilators, antiandrogens, cyclosporins, cyclosporin analogs, antimicrobials, antiflammatories, thyroid hormones, thyroid hormone derivatives, and thyroid hormone analogs, non-selective prostaglandin agonists or antagonists, retinoids, triterpenes, combinations thereof, and others. "Non-selective prostaglandin" agonists and antagonists differ from component A) in that they do not selectively activate the FP receptor, and they may activate other receptors.

[0107] Vasodilators such as potassium channel agonists including minoxidil and minoxidil derivatives such as aminexil and those described in U.S. Pat. Nos. 3,382,247, 5,756,092, 5,772,990, 5,760,043, 5,466,694, 5,438,058, 4,973,474, and cromakalin and diazoxide can be used as optional hair growth stimulants in the composition.

[0108] Examples of suitable antiandrogens include 5α-reductase inhibitors such as finasteride and those described in U.S. Pat. No. 5,516,779, and in Nane et al., Cancer Research 58, "Effects of Some Novel Inhibitors of C17,20-Lyase and 5α-Reductase in vitro and in vivo and Their Potential Role in the Treatment of Prostate Cancer," as well as cyproterone acetate, azelaic acid and its derivatives and those compounds described in U.S. Pat. No. 5,480,913, flutamide, and those compounds described in U.S. Pat. Nos. 5,411,981, 5,565,467, and 4,910,226.

[0109] Antimicrobials include selenium sulfide, ketoconazole, triclocarbon, triclosan, zinc pyrithione, itraconazole, asiatic acid, hinokitiol, mipirocin and those described in EPA 0,680,745, clinaclacin hydrochloride, benzyl peroxide, benzyl peroxide and minocyclin.

[0110] Examples of suitable anti-inflammatory include glucocorticoids such as hydrocortisone, mometasone furoate and prednisolone, nonsteroidal anti-inflammatories including cyclooxygenase or lipooxygenase inhibitors such as those described in U.S. Pat. No. 5,756,092, and benzydamine, salicylic acid, and those compounds described in EPA 0,770,399, published May 2, 1997, WO 94/06434, published Mar. 31, 1994, and FR 2,268,523, published Nov. 21, 1975.

[0111] 3,5,3'-Triiodothyronine is an example of a suitable thyroid hormone.


[0113] Suitable retinoids include isoretinoin, acitretin, and tazarotene.

[0114] Other optional hair growth stimulants for component i) include benzalkonium chloride, benzethonium chloride, phenol, estradiol, chlorpheniramime maleate, chlorophyllin derivatives, cholesterol, salicylic acid, cysteine, methionine, red pepper tincture, benzyl nicotinate, D.L.-menthol, peppermint oil, calcium pantothenate, panthenol, castor oil, prednisolone, resorcinol, chemical activators of protein kinase C, glycosaminoglycan chain cellular uptake inhibitors, inhibitors of glycosidase activity, glycosaminoglycan inhibitors, esters of pyrogallol acid, hexosaccharic acids or acetylated hexosaccharic acids, aryl-substituted ethylenes, N-acetylated amino acids, flavinoids, ascomycin derivatives and analogs, histamine antagonists such as diphenhydramine hydrochloride, triterpenes such as oleanolic acid and ursoic acid and those described in U.S. Pat. Nos. 5,529,769, 5,468,888, 5,631,282, and 5,679,705, JP 10017431, WO 95/35103, JP 09067253, WO 92/09202, JP 6203212, and JP 08193094; saponins such as those described in EP 0,558,509 to Bonne et al., published Sep. 8, 1993 and WO 97/01346 to Bonne et al., published Jan. 16, 1997, proteoglycanase or glycosaminoglycanase inhibitors such as those described in U.S. Pat. Nos. 5,015,470, 5,300,284, and 5,185,325, estrogen agonists and antagonists, pseudotetin, cytokine and growth factor promoters, analogs or inhibitors such as interleukin inhibitors, interleukin-6 inhibitors, interleukin-10 promoters, and tumor necrosis factor inhibitors, vitamins such as vitamin D analogs and parathyroid hormone antagonists, Vitamin B12 analogs and panthotin, interleukin agonists and antagonists, hydroxyacids such as those described in U.S. Pat. No. 5,550,158, benzophenones, and hydantoin anticonvulsants such as phenytoin, and combinations thereof.

[0116] The most preferred activity enhancers are minoxidil and finasteride, most preferably minoxidil. Component ii) is a penetration enhancer that can be added to all of the compositions for systemic administration. The amount of component ii), when present in the composition, is typically 1 to 5%. Examples of penetration enhancers include 2-methyloxandrolone, prop-2-en-2-yl, ethyl-2-hydroxypropionate, hexan-2,5-diol, polyoxymethylene(2)-ethyl ether, di(2-hydroxypropyl) ether, pentan-2,4-diol, acetone, polyoxymethylene(2)-ethyl ether, 2-hydroxypropionic acid, 2-hydroxyoctanoic acid, propan-1-ol, 1,4-dioxane, tetrahydrofuran, butan-1,4-diol, propylene glycol dipalmitate, polypropylene glycol 15 stearyl ether, octyl alcohol, polyethylene glycol ester of oleoyl alcohol, oleoyl alcohol, lauryl alcohol, diocyl adipate, dicaprylyl adipate, di-isopropyl adipate, diisopropyl sebacate, dibutyl sebacate, dimethyl sebacate, dioctyl sebacate, dibutyl sebacate, dioctyl azelate, dibenzyl sebacate, dibutyl phthalate, dibutyl azelate, ethyl myristate, dimethyl azelate, butyl myristate, dibutyl succinate, dicetyl phthalate, decyl oleate, ethyl caproate, ethyl salicylate, isopropyl palmitate, ethyl laurate, 2-ethylhexyl palgargonate, isopropyl isostearate, butyl laurate, benzyl benzoate, butyl benzoate, hexyl laurate, ethyl caprate, ethyl caprylate, butyl stearate, benzyl salicylate, 2-hydroxypropanoic acid, 2-hydroxyoctanoic acid, dimethyl sulfoxide, N,N-dimethyl acetamide, N,N-dimethyl formamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 3-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, phosphoric acid, and alcohols such as isopropyl alcohol, 1,2-dodecylcyclohexan-2-one, omega three fatty acids and fish oils, and combinations thereof.

[0117] In a preferred embodiment of the invention, the prostaglandins are topically administered. Topical compositions that can be applied locally to the skin may be in any form including 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 prostaglandin described above and component B) a carrier. The carrier of the topical composition preferably aids penetration of the prostaglandins into the skin to reach the environment of the hair follicle. Topical compositions preferably further comprise C) one or more of the optional activity enhancers described above.

[0118] The exact amounts of each component in the topical composition for treating hair loss depend on various factors. The amount of component A) depends on the IC_{50} of the prostaglandin selected. IC_{50} means inhibitory concentration 50th percentile. The amount of component A) added to the topical composition is:

\[ IC_{50} \times 10^{-3}\% \text{ of component A) } IC_{50} \times 10^{-3}\]

[0119] where IC_{50} is expressed in nanomolar units. For example, if the IC_{50} of the prostaglandin is 1 nM, the amount of component A) will be 0.001 to 0.01%. If the IC_{50} of the prostaglandin is 10 nM, the amount of component A) will be 0.01 to 0.1%. If the IC_{50} of the prostaglandin is 100 nM, the amount of component A) will be 0.1 to 1.0%. If the IC_{50} of the prostaglandin is 1000 nM, the amount of component A) will be 1.0 to 10%, preferably 1.0 to 5%. If the amount of component A) is outside the ranges specified above (i.e., either higher or lower), efficacy of the treatment may be reduced. IC_{50} can be calculated according to the method in Reference Example 1, below. One skilled in the art can calculate IC_{50} without undue experimentation.

[0120] The topical composition preferably further comprises 1 to 20% component C), and a sufficient amount of component B) such that the amounts of components A), B), and C), combined equal 100%. The amount of B) the carrier employed in conjunction with the prostaglandin is sufficient to provide a practical quantity of composition for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references: Modern Pharmaceuticals, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms, 2nd Ed., (1976).

[0121] Component B) the carrier may comprise a single ingredient or a combination of two or more ingredients. In the topical compositions, component B) is a topical carrier. Preferred topical carriers comprise one or more ingredients selected from the group consisting of water, alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, propylene glycol-2-myristyl propionate, dimethyl isosorbide, combinations thereof, and the like. More preferred carriers include propylene glycol, dimethyl isosorbide, and water.

[0122] The topical carrier may comprise one or more ingredients selected from the group consisting of q) emollients, t) propellants, s) solvents, t) humectants, u) thickeners, v) powders, and w) fragrances in addition to, or instead of, the preferred topical carrier ingredients listed above. One skilled in the art would be able to optimize carrier ingredients for the topical compositions without undue experimentation.

[0123] Ingredient q) is an emollient. The amount of ingredient q) in the topical composition is typically 5 to 95%. Suitable emollients include stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,3-diol, butane-1,3-diol, minik oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isostearic stearate, oleoyl alcohol, isopropyl laurate, hexyl laurate, isobutyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol...
col, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petrolatum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linolate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate, polydimethylsiloxane, and combinations thereof. Preferred emollients include stearyl alcohol and polydimethylsiloxane.

[0124] Ingredient r) is a propellant. The amount of ingredient r) in the topical composition is typically 5 to 95%. Suitable propellants include propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide, and combinations thereof.

[0125] Ingredient s) is a solvent. The amount of ingredient s) in the topical composition is typically 5 to 95%. Suitable solvents include water, ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monomethyl ether, diethylene glycol monobutyl ether, diethylene glycol mono-ethyl ether, dimethylsulfoxide, dimethyl formamide, tetrahydrofuran, and combinations thereof. Preferred solvents include ethyl alcohol.

[0126] Ingredient t) is a humectant. The amount of ingredient t) in the topical composition is typically 5 to 95%. Suitable humectants include glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, solubal collagen, dibutyl phthalate, gelatin, and combinations thereof. Preferred humectants include glycerin.

[0127] Ingredient u) is a thickener. The amount of ingredient u) in the topical composition is typically 0 to 95%.

[0128] Ingredient v) is a powder. The amount of ingredient v) in the topical composition is typically 0 to 95%. Suitable powders include chalk, talc, fillers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate, and combinations thereof.

[0129] Ingredient w) is a fragrance. The amount of ingredient w) in the topical composition is typically 0.001 to 0.5%, preferably 0.001 to 0.1%.

[0130] Component C) the optional activity enhancer is as described above. Any of the i) hair growth stimulants and ii) penetration enhancers may be added to the topical compositions. Preferably, the topical composition comprises 0.01 to 15% of component i) the optional hair growth stimulant. More preferably, the composition comprises 0.1 to 10%, and most preferably 0.5 to 5% of component i). Preferably, the topical composition comprises 1 to 5% of component ii).

[0131] In an alternative embodiment of the invention, the topical composition may be applied to growing hair and skin in the locus of the growing hair to darken to darken hair, reverse hair graying, and thicken the hair. For example, the topical composition may be applied to hair growing on the scalp or eyelashes. The topical composition can be, for example, a cosmetic composition prepared as described above. An example of a composition that may be applied to eyelashes is a mascara. The prostaglandin may be added to mascara compositions known in the art, such as the mascara described in U.S. Pat. No. 5,874,072, which is hereby incorporated by reference. The mascara comprises dd) a water-insoluble material, ee) a water-soluble, film-forming polymer, ff) a wax, gg) a surfactant, and s) a solvent.

[0132] Ingredient dd) is a water-insoluble material selected from the group consisting of acrylate copolymers; styrene/acylate/methacrylate copolymers; acrylic latex; styrene/acrylic ester copolymer latex; polyvinylacetate latex; vinyl acetate/ethylene copolymer latex; styrene-butadiene copolymer latex; polyurethane latex; butadiene/acrylonitrile copolymer latex; styrene/acylate/acrylonitrile copolymer latex; and mixtures thereof, wherein the acrylate copolymers, and the styrene/acylate/methacrylate copolymers additionally comprise ammonia, propylene glycol, a preservative and a surfactant.

[0133] Ingredient ee) is a water-soluble, film-forming polymer. Ingredient ee) is selected from the group consisting of vinyl alcohol/poly(alkyleneoxy)acrylate, vinyl alcohol/vinyl acetate/poly(alkyleneoxy)acrylate, polyethylene oxide, polypropylene oxide, acrylates/octyl-acrylamide copolymers and mixtures thereof.

[0134] Ingredient ff) is a wax. “Wax” means a lower-melting organic mixture or compound of high molecular weight, solid at room temperature and generally similar in composition to fats and oils except that they contain no glycerides. Some are hydrocarbons, others are esters of fatty acids and alcohols. Waxes useful in this invention are selected from the group consisting of animal waxes, vegetable waxes, mineral waxes, various fractions of natural waxes, synthetic waxes, petroleum waxes, ethylene polymers, hydrocarbon types such as Fishech-Tropsch waxes, silicone waxes, and mixtures thereof wherein the waxes have a melting point between 55 and 100°C.


[0136] Ingredient gg) is a pigment. Suitable pigments 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, coated in the Color Index under the reference CI 77891; black, yellow, red and brown iron oxides, coated under references CI 77499, 77492 and, 77491; manganese violet (CI 77742); ultramarine blue (CI 77007); chromium oxide (CI 77288); chromium hydrate (CI 77289); and ferric blue (CI 77510) and mixtures thereof.

[0137] 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
effect on bone loss. Thus, other actives such as vitamin D analogs, hormones, calcium supplements, diphosphonate compounds such as those extensively described in the literature of the Procter & Gamble Company, combinations thereof, and the like may also be administered to patients in need of such treatment in conjunction with the prostaglandins. Dosage levels and means of administration include pulsed-dosing, and are as described in the literature.

Intraocular Pressure

[0149] The prostaglandins used in this invention are also useful in decreasing intraocular pressure. Thus, these prostaglandins are useful in the treatment of glaucoma. This invention further relates to compositions for lowering intraocular pressure. The preferred route of administration for lowering intraocular pressure is topical. Topical pharmaceutical compositions for ocular administration typically comprise A) a prostaglandin, B) a carrier, such as purified water, and one or more ingredients selected from the group consisting of y) sugars such as dextrose, particularly dextran 70, z) cellulose or a derivative thereof, a) a salt, b) disodium EDTA (Edetate disodium), and c) a pH adjusting additive.

[0150] Examples of z) cellulose derivatives suitable for use in the topical pharmaceutical composition for ocular administration include sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and hydroxypropylmethylcellulose. Hydroxypropylcellulose is preferred.

[0151] Examples of a) salts suitable for use in the for use in the topical pharmaceutical composition for ocular administration include sodium chloride, potassium chloride, and combinations thereof.

[0152] Examples of c) pH adjusting additives include HCl or NaOH in amounts sufficient to adjust the pH of the topical pharmaceutical composition for ocular administration to 7.2-7.5.

Methods of the Invention

Hair Loss

[0153] This invention further relates to a method for treating hair loss in mammals. The method comprises administering to a mammal (preferably a human) suffering from hair loss, a prostaglandin described above. For example, a mammal diagnosed with alopecia including male pattern baldness and female pattern baldness can be treated by the methods of this invention. Preferably, a systemic or topical composition comprising A) the prostaglandin and B) a carrier is administered to the mammal. More preferably, the composition is a topical composition comprising A) the prostaglandin, B) the carrier, and C) an optional activity enhancing.

[0154] The dosage of the prostaglandin administered to treat hair loss depends on the method of administration. For systemic administration, (e.g., oral, rectal, nasal, sublingual, buccal, or parenteral), typically, 0.5 mg to 300 mg, preferably 0.5 mg to 100 mg, more preferably 0.1 mg to 10 mg, of a prostaglandin described above is administered per day. These dosage ranges are merely exemplary, and daily administration can be adjusted depending on various factors. The specific dosage of the prostaglandin to be administered, as well as the duration of treatment, and whether the treatment is topical or systemic are interdependent. The dosage and treatment regimen will also depend upon such factors as the specific prostaglandin used, the treatment indication, the efficacy of the compound, the personal attributes of the subject (such as, for example, weight, age, sex, and medical condition of the subject), compliance with the treatment regimen, and the presence and severity of any side effects of the treatment.

[0155] For topical administration (e.g., local application on the skin, liposome delivery systems, or iontophoresis), the topical composition is typically administered once per day. The topical compositions are administered daily for a relatively short amount of time (i.e., on the order of weeks). Generally, 6 to 12 weeks is sufficient. The topical compositions are preferably leave-on compositions. In general, the topical composition should not be removed for at least several hours after administration.

[0156] In addition to the benefits in treating hair loss, the inventors have found that the prostaglandins in the compositions and methods of this invention also darken and thicken hair and may reverse hair graying. This invention further relates to a method for darkening hair, thickening hair, and reversing hair graying. The method comprises applying the topical composition for treating hair loss to hair, to skin in the locus of hair, or both. In a preferred embodiment of the invention, the topical composition, such as the maskara composition described above, is applied to eyelashes.

Bone Disorders

[0157] This invention further relates to methods for treating bone disorders the prostaglandins described above. The method comprises administering to a mammal (preferably a human) suffering from a bone disorder, a prostaglandin described above. For example, a mammal diagnosed with osteoporosis can be treated by the methods of this invention. Preferably, a systemic or topical composition comprising A) the prostaglandin and B) a carrier is administered to the mammal. The preferred routes of administration for treating bone disorders are transdermal, intranasal, rectal, sublingual, and oral.

[0158] The dosage range of the prostaglandin for systemic administration to treat bone disorders is from about 0.01 to about 1000 μg/kg body weight, preferably from about 0.1 to about 100 μg per body weight, most preferably form about 1 to about 50 μg/kg body weight per day. The transdermal dosages will be designed to attain similar serum or plasma levels, based on 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 nanograms/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, weekly or monthly accumulated dosages may also be used to calculate the clinical requirements.

[0159] Dosages may be varied based on the patient being treated, the condition being treated, the severity of the condition being treated, the route of administration, etc. to achieve the desired effect.

Intraocular Pressure

[0160] The prostaglandins of the present invention are also useful in decreasing intraocular pressure. Thus, these pros-
taglandins are useful in the treatment of glaucoma. This invention further relates to a method for lowering intraocular pressure in mammals. The method comprises administering to a mammal (preferably a human) a prostaglandin described above. For example, a mammal diagnosed with glaucoma can be treated by the methods of this invention. The preferred route of administration for treating glaucoma is topical. Preferably, a topical composition for ocular administration described above is administered to the mammal. The topical composition for ocular administration is typically administered once per day. The topical compositions are administered daily for a relatively short amount of time (i.e., on the order of weeks). Generally, 6 to 12 weeks is sufficient.

EXAMPLES

[0161] These examples are intended to illustrate the invention to those skilled in the art and should not be interpreted as limiting the scope of the invention set forth in the claims.

Reference Example 1

Radioligand Binding Assay

[0162] IC_{50} of a prostaglandin can be determined relative to PGF_{2α} using the Radioligand Binding Assay. As a control, the IC_{50} for PGF_{2α} itself should be no lower than 1.0 nM and no higher than 5.0 nM.

[0163] In this assay, COS-7 cells are transiently transfected with the hF recombinant plasmid using LipofectAMINE Reagent. Forty-eight hours later, the transfected cells are washed with Hank’s Balanced Salt Solution (HBSS, without CaCl_{2}, MgCl_{2}, MgSO_{4} or phenol red). The cells are detached with versene, and HBSS is added. The mixture is centrifuged at 200 g for 10 minutes, at 4°C, to pellet the cells. The pellet is resuspended in Phosphate-Buffered Saline-EDTA buffer (PBS; 1 mM EDTA; pH 7.4; 4°C). The cells are disrupted by nitrogen cavitation (Parr model 4639), at 800 psi, for 15 minutes at 4°C. The mixture is centrifuged at 1000 g for 10 minutes at 4°C. The supernatant is centrifuged at 100000 g for 60 minutes at 4°C. The pellet is resuspended to 1 mg protein/mL TME buffer (50 mM Tris; 10 mM MgCl_{2}; 1 mM EDTA; pH 6.0; 4°C) based on protein levels measured using the Pierce BCA Protein Assay kit. The homogenate is mixed for 10 seconds using a Kinematica POLYTRON ® (available from KINE-MATICA AG, Luzernstrasse147A CH-6014 Littau, Switzerland). The membrane preparations are then stored at -80°C, until thawed for assay use.

[0164] The receptor competition binding assays are developed in a 96 well format. Each well contains 100 g of hF membrane, 5 nM (3H) PGF_{2α}, and the various competing compounds in a total volume of 200 L. The plates are incubated at 23°C for 1 hour. The incubation is terminated by rapid filtration using the Packard Filtrarem 196 harvester through Packard UNILIT® GF/B filters (available from Packard Instrument Co., Inc. of Downers Grove Illinois) pre-wetted with TME buffer. The filter is washed four times with TME buffer. Packard Microscint 20, a high efficiency liquid scintillation cocktail, is added to the filter plate wells and the plates remain at room temperature for three hours prior to counting. The plates are read on a Packard TOP-COUNT® Microplate Scintillation Counter (also available from Packard Instrument Co., Inc.)

Reference Example 2

Telogen Conversion Assay

[0165] Prostaglandins are tested for their potential to grow hair using the Telogen Conversion Assay. The Telogen Conversion Assay measures the potential of a prostaglandin to convert mice in the resting stage of the hair growth cycle (“telogen”), to the growth stage of the hair growth cycle (“anagen”).

[0166] Without intending to be limited by theory, there are three principal phases of the hair growth cycle: anagen, catagen, and telogen. It is believed that there is a longer telogen period in C3H mice (Harlan Sprague Dawley, Inc., Indianapolis, Ind.) from approximately 40 days of age until about 75 days of age, when hair growth is synchronized. It is believed that after 75 days of age, hair growth is no longer synchronized. Wherein about 40 day-old mice with dark fur (brown or black) are used in hair growth experiments, melanogenesis occurs along with hair (fur) growth wherein the topical application of hair growth inducers are evaluated. The Telogen Conversion Assay herein is used to screen prostaglandins for potential hair growth by measuring melanogenesis.

[0167] Three groups of 44 day-old C3H mice are used: a vehicle control group, a positive control group, and a test prostaglandin group, wherein the test prostaglandin group is administered a prostaglandin used in the method of this invention. The length of the assay is 24 days with 15 treatment days (wherein the treatment days occur Mondays through Fridays). Day 1 is the first day of treatment. A typical study design is shown in Table 4 below. Typical dosage concentrations are set forth in Table 3, however the skilled artisan will readily understand that such concentrations may be modified.

<table>
<thead>
<tr>
<th>Assay Parameters</th>
<th>Group</th>
<th>Animal</th>
<th>Compound</th>
<th>Concentration</th>
<th>Application volume</th>
<th>Length of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>10</td>
<td>Test</td>
<td>0.01% in vehicle**</td>
<td>400 μL topical</td>
<td>26 days</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10-20</td>
<td>Positive</td>
<td>0.01% in vehicle**</td>
<td>400 μL topical</td>
<td>26 days</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>21-30</td>
<td>Vehicle</td>
<td>N/A</td>
<td>400 μL topical</td>
<td>26 days</td>
</tr>
</tbody>
</table>

*T3 is 3,5,3'-triiodothyronine.
**The vehicle is 60% ethanol, 20% propylene glycol, and 20% dimethyl isosorbide.

[0168] (commercially available from Sigma Chemical Co., St. Louis, Mo.).

[0169] The mice are treated topically Monday through Friday on their lower back (base of tail to the lower rib). A pipettor and tip are used to deliver 400 μL to each mouse’s back. The 400 μL application is applied slowly while moving hair on the mouse to allow the application to reaches the skin.

[0170] While each treatment is being applied to the mouse topically, a visual grade of from 0 to 4 will be given to the skin color in the application area of each animal. As a mouse converts from telogen to anagen, its skin color will become
more bluish-black. As indicated in Table 5, the grades 0 to 4 represent the following visual observations as the skin progresses from white to bluish-black.

**TABLE 5**

<table>
<thead>
<tr>
<th>Visual Observation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitish Skin Color</td>
<td>0</td>
</tr>
<tr>
<td>Skin is light gray (indications of initiation of anagen)</td>
<td>1</td>
</tr>
<tr>
<td>Appearance of Blue Spots</td>
<td>2</td>
</tr>
<tr>
<td>Blue Spots are aggregating to form one large blue area</td>
<td>3</td>
</tr>
<tr>
<td>Skin is dark blue (almost black) with color covering majority of treatment area (indications of mouse in full anagen)</td>
<td>4</td>
</tr>
</tbody>
</table>

Reference Example 3

Ovariectomized Rat Assay

[0171] Bone activity of the prostaglandins can be conveniently demonstrated using an assay designed to test the ability of the prostaglandins to increase bone volume, mass, or density. An example of such assays is the ovariectomized rat assay.

[0172] In the ovariectomized rat assay, six-month old rats are ovariectomized, aged 2 months, and then dosed once a day subcutaneously with a prostaglandin. Upon completion of the study, bone mass and/or density can be measured by dual energy x-ray absorptometry (DXA) or peripheral quantitative computed tomography (pQCT), or micro computed tomography (μCT). Alternatively, static and dynamic histomorphometry can be used to measure the increase in bone volume or formation.

Reference Example 4

Pharmacological Activity for Glaucoma Assay

[0173] Pharmacological activity for glaucoma can be demonstrated using assays designed to test the ability of the subject compounds to decrease intraocular pressure. Examples of such assays are described in the following reference, incorporated herein: C. Hijbeirs, G.


Example 1

[0175] Compositions for topical administration are made, comprising:

<table>
<thead>
<tr>
<th>Component</th>
<th>Ex. 1-1</th>
<th>Ex. 1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin (wt %)</td>
<td>0.42</td>
<td>1.14</td>
</tr>
<tr>
<td>IC_{50} the PGF (μM)</td>
<td>4.2</td>
<td>114</td>
</tr>
<tr>
<td>Ethanol (wt %)</td>
<td>89.74</td>
<td>89.32</td>
</tr>
<tr>
<td>Propylene Glycol (wt %)</td>
<td>19.92</td>
<td>19.77</td>
</tr>
<tr>
<td>Dimethyl Isosorbide (wt %)</td>
<td>19.92</td>
<td>19.77</td>
</tr>
</tbody>
</table>

[0176] The prostaglandins in the topical compositions are as follows:

Example 2

[0177] A human male subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 6 weeks, one of the above compositions is daily administered topically to the subject to induce hair growth.

Example 3


[0179] A human male subject suffering from male pattern baldness is treated each day with the above composition. Specifically, for 6 weeks, the above composition is administered topically to the subject.

Example 3

[0180] Shampoos are made, comprising:

<table>
<thead>
<tr>
<th>Component</th>
<th>Ex. 3-1</th>
<th>Ex. 3-2</th>
<th>Ex. 3-3</th>
<th>Ex. 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonium Lauril 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>Cocomide MEA</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Ethylene Glycol Distearte</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Glycerol</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Glyceryl Alcohol</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Glyceryl Alcohol</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</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>0.5%</td>
<td>0.25%</td>
<td>—</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>0.2%</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Sucrose Polymers of Cottonse</td>
<td>3%</td>
<td>3%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fatty Acid</td>
<td>2%</td>
<td>2%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sucrose Polymers of Behenate</td>
<td>3%</td>
<td>3%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fatty Acid</td>
<td>3%</td>
<td>3%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fatty Acid</td>
<td>3%</td>
<td>3%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Polymethyl Siloxane</td>
<td>—</td>
<td>—</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Cocamimopropl Betaine</td>
<td>1%</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>
</tbody>
</table>
-continued

<table>
<thead>
<tr>
<th>Component</th>
<th>Ex. 3-1</th>
<th>Ex. 3-2</th>
<th>Ex. 3-3</th>
<th>Ex. 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decyl Polyglucose</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>DMDM Hydantoin</td>
<td>0.15%</td>
<td>0.15%</td>
<td>0.15%</td>
<td>0.15%</td>
</tr>
<tr>
<td>PGO having IC₅₀ of 42 nM</td>
<td>0.42%</td>
<td>0.42%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PGO having IC₅₀ of 114 nM</td>
<td>0.11%</td>
<td>0.11%</td>
<td>0.11%</td>
<td>0.11%</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
<td>2%</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>

[0181] The prostaglandins are the same as in Example 1.

[0182] 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.

**Example 4**

[0183] A mascara composition is prepared. The composition comprises:

<table>
<thead>
<tr>
<th>Component</th>
<th>% W/W</th>
</tr>
</thead>
<tbody>
<tr>
<td>WATER, DEIONIZED, USP</td>
<td>q.s.</td>
</tr>
<tr>
<td>BLACK [080] MUNICONIZED TYPE</td>
<td>10.00</td>
</tr>
<tr>
<td>GLYCERYL MONOSTEARATE (2400 TYPE)</td>
<td>8.50</td>
</tr>
<tr>
<td>CI8–36 ACID TRIGLYCERIDE</td>
<td>5.50</td>
</tr>
<tr>
<td>STEARIC ACID, TRIPLE PRESSED, LIQUID</td>
<td>4.00</td>
</tr>
<tr>
<td>ETHYL ALCOHOL SD 40-B, 190 PROOF/SEIAL #:</td>
<td>4.00</td>
</tr>
<tr>
<td>BEEF WAX WHITE, FLAKES</td>
<td>3.25</td>
</tr>
<tr>
<td>SHELLAC, NF</td>
<td>3.00</td>
</tr>
<tr>
<td>LECITHIN, GRANULAR (TYPE 6450)</td>
<td>2.50</td>
</tr>
<tr>
<td>TRIETHANOLAMINE 99% - TANK</td>
<td>2.47</td>
</tr>
<tr>
<td>PARAFFIN WAX</td>
<td>2.25</td>
</tr>
<tr>
<td>PARAFFIN WAX 118/125</td>
<td>2.25</td>
</tr>
<tr>
<td>CARNABUA WAX, NF</td>
<td>2.00</td>
</tr>
<tr>
<td>POTASSIUM Cetyl PHOSPHATE</td>
<td>1.00</td>
</tr>
<tr>
<td>PHENOXYETHANOL</td>
<td>0.80</td>
</tr>
<tr>
<td>OLEIC ACID NF</td>
<td>0.75</td>
</tr>
<tr>
<td>DL-PANTHENOL</td>
<td>0.35</td>
</tr>
<tr>
<td>PVP/VA COPOLYMER</td>
<td>0.25</td>
</tr>
<tr>
<td>METHYL PARABEN, NF</td>
<td>0.20</td>
</tr>
<tr>
<td>DIACONTINYL UREA</td>
<td>0.20</td>
</tr>
<tr>
<td>SIMEUTICONE</td>
<td>0.20</td>
</tr>
<tr>
<td>ETHYL PARABEN NF</td>
<td>0.15</td>
</tr>
<tr>
<td>PENTAERYTHRITYL HYDROGENATED ROSINATE</td>
<td>0.15</td>
</tr>
<tr>
<td>PROPYL PARABEN, NF</td>
<td>0.10</td>
</tr>
<tr>
<td>TRISODIUM EDTA</td>
<td>0.10</td>
</tr>
<tr>
<td>PROSTAGLANDIN having IC₅₀ of 114 nM</td>
<td>0.11%</td>
</tr>
</tbody>
</table>

[0184] The prostaglandin is the same as in Example 1-2.

[0185] A human female subject applies the composition each day. Specifically, for 6 weeks, the above composition is administered topically to the subject to darken and thicken eyelashes.

**Example 5**

[0186] A pharmaceutical composition in the form of a tablet is prepared by conventional methods, such as mixing and direct compaction, formulated as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg per tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin</td>
<td>5</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>100</td>
</tr>
<tr>
<td>Sodium Starch Glycollate</td>
<td>30</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>3</td>
</tr>
</tbody>
</table>

[0187] The prostaglandin is the same as in Example 1-2.

[0188] When administered orally once daily, the above composition substantially increases bone volume in a patient suffering from osteoporosis.

**Example 6**

[0189] A pharmaceutical compositions in liquid form is prepared by conventional methods, formulated as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin</td>
<td>1 mg</td>
</tr>
<tr>
<td>Phosphate buffered physiological saline</td>
<td>10 ml</td>
</tr>
<tr>
<td>Methyl Paraben</td>
<td>0.05 ml</td>
</tr>
</tbody>
</table>

[0190] The prostaglandin used is the same as in Example 1-2.

[0191] When 1.0 ml of the above composition is administered subcutaneously once daily, the above composition substantially increases bone volume in a patient suffering from osteoporosis.

**Example 7**

[0192] A topical pharmaceutical composition 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>Prostaglandin</td>
<td>0.004</td>
</tr>
<tr>
<td>Dextran 70</td>
<td>0.1</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose</td>
<td>0.3</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>0.77</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>0.12</td>
</tr>
<tr>
<td>Disodium EDTA (Edetate disodium)</td>
<td>0.05</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td>0.01</td>
</tr>
<tr>
<td>HCl and/or NaOH</td>
<td>pH 7.2–7.5</td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s. to 100%</td>
</tr>
</tbody>
</table>

[0193] The prostaglandin is the same as in Example 1-2.

[0194] When the above composition is administered once daily for 6 to 12 weeks, it lowers intraocular pressure in a patient suffering from glaucoma.

**Effects of the Invention**

[0195] The compositions and methods herein provide a cosmetic benefit with respect to hair growth and appearance in subjects desiring such treatment. The compositions and methods herein also provide pharmaceutical benefits with
What is claimed is:

1. A 2-decarboxy-2-phosphinico prostaglandin analog having the structure:

   ![Chemical Structure](image)

   wherein

   - $R^3$ is selected from the group consisting of a hydrogen atom, lower monovalent hydrocarbon groups, and lower heterogenous groups;
   - $R^2$ is selected from the group consisting of a hydrogen atom, a monovalent hydrocarbon group, a substituted monovalent hydrocarbon group, a heterogenous group, a substituted heterogenous group, a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group;
   - $R^1$ is selected from the group consisting of an oxygen atom, a sulfur atom, and NH;
   - $R^3$ is selected from the group consisting of an oxygen atom and a sulfur atom;
   - $R^2$ is a divalent group selected from the group consisting of a hydrocarbon group, a substituted hydrocarbon group, a heterogenous group, and a substituted heterogenous group;
   - bond a is selected from the group consisting of a single bond, a trans double bond, and a triple bond;
   - $R^6$ is a divalent group selected from the group consisting of $-\text{C(O)}-$ and $-\text{C}(\text{R}^0)\text{O}(\text{R}^0)-$;
   - $R^7$ is selected from the group consisting of a divalent group having the formula $-(\text{CR}^0\text{R}^0))_{p} \text{X} \text{CR}^0\text{R}^0)_{q}$, wherein $p$ is an integer from 0 to 3 and $q$ is an integer from 0 to 3, and wherein $X$ is selected from the group consisting of an oxygen atom, a divalent hydrocarbon group, a sulfur atom, SO, SO$_2$, and NR$^3$;
   - $R^8$ is selected from the group consisting of a methyl group or a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group;
   - $R^9$ is selected from the group consisting of a hydrogen atom and a lower monovalent hydrocarbon group; and
   - $R^{10}$ is a lower monovalent hydrocarbon group.

2. A composition for treating hair loss comprising:
   A) an active ingredient selected from the group consisting of 2-decarboxy-2-phosphinico derivatives of prostaglandins; optical isomers, diastereomers, and enantiomers of the 2-decarboxy-2-phosphinico derivatives; pharmaceutically-acceptable salts of the 2-decarboxy-2-phosphinico derivatives; biohydrolyzable amides, esters, and imides of the 2-decarboxy-2-phosphinico derivatives; and combinations thereof; and
   B) a carrier.

3. The composition of claim 2, wherein the 2-decarboxy-2-phosphinico derivative has a structure selected from the group consisting of:

   ![Chemical Structure](image)

   wherein $R^1$ is selected from the group consisting of a hydrogen atom, and lower monovalent hydrocarbon groups, and lower heterogenous groups;

   - $R^2$ is selected from the group consisting of a hydrogen atom, a monovalent hydrocarbon group, a substituted monovalent hydrocarbon group, a heterogenous group, a substituted heterogenous group, a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group;
   - $R^3$ is selected from the group consisting of an oxygen atom, a sulfur atom, and NH;
   - $R^4$ is selected from the group consisting of an oxygen atom and a sulfur atom;
   - $R^5$ is a divalent group selected from the group consisting of a hydrocarbon group, a substituted hydrocarbon group, a heterogenous group, and a substituted heterogenous group;
   - bond a is selected from the group consisting of a single bond, a trans double bond, and a triple bond;
   - $R^6$ is a divalent group selected from the group consisting of $-\text{C(O)}-$ and $-\text{C}(\text{R}^0)\text{O}(\text{R}^0)-$;
   - $R^7$ is selected from the group consisting of a divalent group having the formula $-(\text{CR}^0\text{R}^0))_{p} \text{X} \text{CR}^0\text{R}^0)_{q}$, wherein $p$ is an integer from 0 to 3 and $q$ is an integer from 0 to 3, and wherein $X$ is selected from the group consisting of an oxygen atom, a divalent hydrocarbon group, a sulfur atom, SO, SO$_2$, and NR$^3$;
   - $R^8$ is selected from the group consisting of a methyl group or a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group;
   - $R^9$ is selected from the group consisting of a hydrogen atom and a lower monovalent hydrocarbon group; and
   - $R^{10}$ is a lower monovalent hydrocarbon group.


group, a heterogeneous group, and a substituted heterogeneous group; with the proviso that when \( R^2 \) is a heterogeneous group, \( R^2 \) has only one heteroatom, which is selected from the group consisting of oxygen, sulfur, and nitrogen;

bond \( a \) is selected from the group consisting of a single bond, a trans double bond, and a triple bond;

\( R^2 \) is a divalent group selected from the group consisting of \(-\text{C(O)}-\) and \(-\text{C(OR)}-\);

\( R^2 \) is selected from the group consisting of a divalent group having the formula \(-\text{C}(R^1(R^2))_p-\text{H}(R^2)_q\), wherein \( p \) is an integer from 0 to 3 and \( q \) is an integer from 0 to 3, and wherein \( X \) is selected from the group consisting of an oxygen atom, a divalent hydrocarbon group, a sulfur atom, \( \text{SO}, \text{SO}_2 \), and \( \text{NR}^3;\)

\( R^2 \) is selected from the group consisting of a methyl group, a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, a substituted heteroaromatic group;

\( R^2 \) is selected from the group consisting of a hydrogen atom and a lower monovalent hydrocarbon group; and

\( R^{O} \) is selected from the group consisting of a hydrogen atom and a lower monovalent hydrocarbon group.

4. The composition of claim 3, wherein \( R^2 \) is selected from the group consisting of a hydrogen atom, an alkyl group, a halogenated hydrocarbon group, \( \text{CH}_2\text{CH}_2\text{OH} \), and \( \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \).

5. The composition of claim 3, wherein \( R \) is selected from the group consisting of \( \text{H, CH}_3\text{CO}_2\text{H, CH}_2\text{O}(\text{O})\text{NH}_2\text{OH, methyl, CF}_3 \), ethyl, \( \text{n-propyl, isopropyl, CH}_2\text{CH}_2\text{OH, CH}_3\text{CH}(\text{OH})\text{CH}_2\text{OH, benzyl, and t-butyl}. \)

6. The composition of claim 3, wherein \( R^2 \) is selected from the group consisting of an oxygen atom and \( \text{NH} \).

7. The composition of claim 3, wherein \( R^2 \) is an oxygen atom.

8. The composition of claim 3, wherein \( R^2 \) has 1 to 5 member atoms.

9. The composition of claim 3, wherein \( R^2 \) is \(-\text{C(H)(OH)-}\).

10. The composition of claim 3, wherein \( X \) is selected from the group consisting of a single bond, a trans double bond, a triple bond, an oxygen atom, a sulfur atom, and \( \text{NR}^3 \).

11. The composition of claim 3, wherein \( R^2 \) is selected from the group consisting of a monocyclic carbocyclic group, a substituted monocyclic carbocyclic group, a monocyclic heterocyclic group, a substituted monocyclic heterocyclic group, aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group.

12. The composition of claim 3, wherein \( R^2 \) is a hydrogen atom.

13. The composition of claim 3, wherein \( R^{O} \) is a hydrogen atom.

14. The composition of claim 3, wherein the 2-decarboxy-2-phosphinico derivative has the structure:

wherein, \( R^1 \), \( R^2 \), \( R^3 \), \( R^4 \), \( R^5 \), \( R^6 \), \( R^7 \), \( R^8 \), and bond \( a \) are as described above.

15. The composition of claim 2, wherein component B) comprises an ingredient selected from the group consisting of: \( q \) emollients, \( r \) propellants, \( s \) solvents, \( t \) humectants, \( u \) thickeners, \( v \) powders, \( w \) fragrances, water, alcohols, aloes vera gel, allantoin, glycercin, vitamin A and E oils, mineral oil, propylene glycol, polypropylene glycol-2 myrist steryl propionate, dimethyl isosorbide, and combinations thereof.

16. The composition of claim 2, further comprising component C) an activity enhancer selected from the group consisting of: \( i \) a hair growth stimulant, \( ii \) a penetration enhancer, and combinations thereof.

17. The composition of claim 16, wherein component A) is present in the composition in an amount of: \( 1\text{C}_{200}\times10^{-2} \geq % \) of component A) \( \geq IC_{50}\times10^{-2} \), where \( IC_{50} \) is expressed in nanomolar units; component C) is present in an amount of 1 to \( 20\% \) component C), and a sufficient amount of component B) is present such that the amounts of components A), B), and C), combined equal 100%.

18. The composition of claim 2, wherein component A) is present in the composition in an amount of: \( 1\text{C}_{200}\times10^{-2} \geq % \) of component A) \( \geq IC_{50}\times10^{-2} \), where \( IC_{50} \) is expressed in nanomolar units.

19. A method for treating hair loss comprising administering to a mammal suffering from hair loss, a composition comprising:

A) an active ingredient selected from the group consisting of 2-decarboxy-2-phosphinico derivatives of prostaglandins; optical isomers, dia stereomers, and enantiomers of the 2-decarboxy-2-phosphinico derivatives; pharmaceutically acceptable salts of the 2-decarboxy-2-phosphinico derivatives; biohydrolyzable amides, esters, and imides of the 2-decarboxy-2-phosphinico derivatives; and combinations thereof.

20. The method of claim 19, wherein the 2-decarboxy-2-phosphinico derivative has a structure selected from the group consisting of:
wherein R is selected from the group consisting of a hydrogen atom, and lower monovalent hydrocarbon groups, and lower heterogeneous groups;

R' is selected from the group consisting of a hydrogen atom, a monovalent hydrocarbon group, a substituted monovalent hydrocarbon group, a heterocyclic group, a substituted heterocyclic group, a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group;

R is selected from the group consisting of an oxygen atom, a sulfur atom, and NH;

R is selected from the group consisting of an oxygen atom and a sulfur atom;

R is a divalent group selected from the group consisting of a hydrocarbon group, a substituted hydrocarbon group, a heterocyclic group, a substituted heterocyclic group; with the proviso that when R is a heterocyclic group, R has only one heteroatom, which is selected from the group consisting of oxygen, sulfur, and nitrogen;

bond a is selected from the group consisting of a single bond, a trans double bond, and a triple bond;

R is a divalent group selected from the group consisting of —O— and —(OH2)(OR2)—;

R is selected from the group consisting of a divalent group having the formula —(CR(R'))2—X—(CR(R'))2—, wherein p is an integer from 0 to 3 and q is an integer from 0 to 3, and wherein X is selected from the group consisting of an oxygen atom, a divalent hydrocarbon group, a sulfur atom, SO2, and NR2;

R is selected from the group consisting of a methyl group, a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, a substituted heteroaromatic group;

R is selected from the group consisting of a hydrogen atom and a lower monovalent hydrocarbon group; and

R1 is selected from the group consisting of a hydrogen atom and a lower monovalent hydrocarbon group.

21. The method of claim 19, wherein the composition is administered by a route selected from the group consisting of systemic and topical routes.

22. The method of claim 21, wherein the composition is a topical composition in a form selected from the group consisting of solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, and skin patches.

23. The method of claim 22, wherein the composition is a topical composition further comprising (i) a topical carrier, wherein the topical carrier comprises an ingredient selected from the group consisting of q emollients, r propellants, s solvents, t humectants, u thickeners, v powders, w fragrances, water, alcohol, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, dimethyl isosorbide, polypropylene glycol-2 myristyl propionate, and combinations thereof.

24. The method of claim 19, wherein the composition further comprises (i) an activity enhancer selected from the group consisting of j a hair growth stimulant, ii) a penetration enhancer, and combinations thereof.

25. The method of claim 24, wherein component i) is selected from the group vasodilator, an antiandrogen, a cyclosporin, a cyclosporin analog, an antimicrobial, an anti-inflammatory, a thyroid hormone, a thyroid hormone derivative, and a thyroid hormone analog, a non-selective prostaglandin agonist, a non-selective prostaglandin antagonist, a retinoid, a triterpene, and combinations thereof.

26. The method of claim 24, wherein component ii) is selected from the group consisting of 2-methylpropan-2-ol, propan-2-ol, ethyl-2-hydroxypropanoate, hexan-2,5-diol, polyoxyethylene(2) ethyl ether, di(2-hydroxypropyl) ether, pentan-2,4-diol, acetone, polyoxyethylene(2) methyl ether, 2-hydroxypropionic acid, 2-hydroxyoctanoic acid, propane-1,1,4-dioxane, tetrahydrofuran, butan-1,4-diol, propylene glycol dipalmitate, poloxamers, polyoxyethylene 15 stearyl ether, octyl alcohol, polyoxyethylene ester of oleyl alcohol, oleyl alcohol, lauryl alcohol, diocetyl adipate, dicapryl adipate, di-isopropyl adipate, di-isopropyl sebacate, dibutyl sebacate, diethyl sebacate, dimethyl sebacate, diocetyl sebacate, dibutyl sebacate, diocetyl azelate, dibenzyl sebacate, diethyl phthalate, dibutyl azelate, ethyl myristate, dimethyl azelate, butyl myristate, dibutyl succinate, didecyl phthalate, decyl oleate, ethyl caproate, ethyl salicylate, isopropyl palmitate, ethyl laurate, 2-ethylhexyl palmitate, isopropyl isostearate, butyl laurate, benzyl benzoate, butyl benzoate, hexyl laurate, ethyl caprate, ethyl caprylate, butyl stearate, benzyl salicylate, 2-hydroxypropanoic acid, 2-hydroxyoctanoic acid, dimethyl sulfoxide, N,N-dimethyl acetamide, N,N-dimethyl formamide, 2-pyridolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyridolidone, 1-ethyl-2-pyridolidone, phosphine oxides, sugar esters, tetrahydrofurfural alcohol, urea, diethyl-m-toluamide, 1-dodecylazacycloheptan-2-one, and combinations thereof.

27. The method of claim 21, wherein the composition is a topical composition locally administered on the skin once per day.

28. The method of claim 27, wherein the composition is administered once per day for 6 to 12 weeks.
29. A mascara composition comprising:
A) an active ingredient selected from the group consisting of 2-decarboxy-2-phosphinico derivatives of prostaglandins; optical isomers, diastereomers, and enantiomers of the 2-decarboxy-2-phosphinico derivatives; pharmaceutically-acceptable salts of the 2-decarboxy-2-phosphinico derivatives; biohydrolyzable amides, esters, and imides of the 2-decarboxy-2-phosphinico derivatives; and combinations thereof;
bd) a water-insoluble material,
ce) a water-soluble, film-forming polymer,
df) a wax;
o) a surfactant;
ng) pigment; and
s) a solvent.

30. A method for darkening and thickening hair comprising applying to growing hair and skin, a composition comprising:
A) an active ingredient selected from the group consisting of 2-decarboxy-2-phosphinico derivatives of prostaglandins; optical isomers, diastereomers, and enantiomers of the 2-decarboxy-2-phosphinico derivatives; pharmaceutically-acceptable salts of the 2-decarboxy-2-phosphinico derivatives; biohydrolyzable amides, esters, and imides of the 2-decarboxy-2-phosphinico derivatives; and combinations thereof; and
B) a carrier.

* * * * *