Title: METHOD OF TREATING HAIR LOSS USING MULTIVALENT KETOAMIDES AND AMIDES

Abstract: The present disclosure describes methods and compounds useful for treating hair loss in mammals, including arresting and/or reversing hair loss and promoting hair growth. The methods comprise administering a compound having a structure as described herein and a pharmaceutically-acceptable carrier. The compounds herein have the structure: M-L-Q wherein M and Q are each, independently, radicals of structure (I).
METHOD OF TREATING HAIR LOSS USING MULTIVALENT KETOAMIDES AND AMIDES

FIELD OF THE INVENTION

The present invention relates to methods for treating hair loss in mammals, including arresting and/or reversing hair loss and promoting hair growth.

BACKGROUND OF THE INVENTION

Hair loss is a common problem which occurs, for example, through natural processes or is often 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 regrowth which causes partial or full baldness.

As is well-known in the art, hair growth occurs by a cycle of activity which involves alternating periods of growth and rest. This cycle is often divided into three main stages which are known as anagen, catagen, and telogen. Anagen is the growth phase of the cycle and may be 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 is ceased. The next phase, telogen, is often 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. This cycle is repeated throughout hair growth. Wherein 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.

There have been many attempts in the literature to invoke the regrowth of hair 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.).

There are conflicting reports, however, regarding the ability of minoxidil to grow hair to any significant extent. In fact, early clinical studies investigating decreased blood pressure via the use of minoxidil did not even mention hypertrichosis (hair growth) as a side effect. See
Dormois et al., “Minoxidil in Severe Hypertension: Value When Conventional Drugs Have Failed”, American Heart Journal, Vol. 90, pp. 360 - 368 (1975). Indeed, the manufacturers of minoxidil have reported only limited hair growth in a portion of patients using minoxidil. See, e.g., Physician’s Desk Reference®, 49th Ed. (1995), p. 2580. Furthermore, serious side effects of minoxidil are possible, including vasodilation (which leads to retention of fluid around the heart and increased heart rate), difficulty in breathing, and weight gain. Physician’s Desk Reference®, 49th Ed. (1995), p. 2581.

Furthermore, while early indicators show that Propecia® may be more effective than Rogaine®, patients using Propecia® are also experiencing limited hair growth. See The New England Journal of Medicine, Vol. 338, No. 9, February 26, 1998. Furthermore, potential side effects of Propecia® are serious. Propecia® may cause impotence, decreased sexual drive, decreased volume of ejaculate, breast tenderness and enlargement, and hypersensitivity reactions, including lip swelling and skin rash. Furthermore, Propecia® is not indicated for women and children. In fact, women who are pregnant or potentially pregnant should not even handle crushed or broken tablets containing the drug. See Physician’s Desk Reference®, 52nd Ed. (1998), p. 1737 and The New England Journal of Medicine, Vol. 338, No. 9, February 26, 1998.

Res., Vol. 288, pp. 408 - 410 (1996). However, use of these compounds as hair growth actives may not be desirable due to their striking potency as immunosuppressive agents.

FK506 is a complex, macrocyclic molecule having the following structure:


However, excitement related to the hypertrichotic activities of cyclosporin A and FK506 was historically somewhat quelled by the lack of reports of hypertrichosis by various non-macro cyclic immunosuppressive and non-immunosuppressive compounds which are less complex in structure than FK506. Only recently has it been reported that certain non-immunosuppressive analogs of FK506 have hypertrichotic potential. See Hamilton et al., WO 98/55090, assigned to Guilford Pharmaceuticals Inc., published December 10, 1998.

Divalent ketoamide analogs of such FK506 analogs have been reported in, for example, Keenan et al., “Synthesis and Activity of Bivalent FKBP12 Ligands for the Regulated Dimerization of Proteins”, Bioorganic & Medicinal Chemistry, Vol. 6, pp. 1309 - 1335 (1998); Holt et al., WO 97/31898, assigned to Ariad Gene Therapeutics, Inc., published September 4, 1997; and Holt et al., WO 97/31899, assigned to Ariad Gene Therapeutics, Inc., published
September 4, 1997. However, there are no reports of utility of these types of compounds for treatment of hair loss.

Surprisingly, the present inventors have discovered a class of divalent amides and ketoamides which arrest and / or reverse hair loss or promote hair growth but do not share the macrocyclic structure of FK506. The present inventors have further discovered that compounds among this class invoke hair growth yet are surprisingly non-immunosuppressive or are nominally immunosuppressive. The minimized and / or absent immunosuppressive activity of these hypertrichotic compounds are distinct advantages as compared to the immunosuppressive compounds cyclosporin A and FK506.

**SUMMARY OF THE INVENTION**

The present invention relates to methods for treating hair loss comprising administering compounds which have been found by the present inventors to be particularly useful for treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth. The compounds utilized in the present method have the structure:

\[ M-L-Q \]

and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein \( M \) and \( Q \) are each, independently, radicals of structure I; wherein structure I is:

\[
\begin{align*}
(\text{h}) & \\
\text{N} & \\
\text{O} & \\
\text{X} & \\
\text{R}_1 & \\
\text{G} & \\
\end{align*}
\]

wherein \( G, X, R_1, \) and \( n \) are defined herein.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention relates to methods of using compounds and compositions to treat hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth.

In addition to discovering that the present compounds are useful for treating hair loss, the present inventors have also surprisingly discovered that immunosuppression is not required for hair growth stimulation. The present inventors have further discovered compounds that are useful for treating hair loss but are surprisingly non-immunosuppressive. Preferred compounds
useful in the methods of the present invention are therefore, as defined herein, non-immunosuppressive.

Publications and patents are referred to throughout this disclosure. All references cited herein are hereby incorporated by reference.

All percentages, ratios, and proportions used herein are by weight unless otherwise specified.

In the description of the invention various embodiments and/or individual features are disclosed. As will be apparent to the ordinarily skilled practitioner all combinations of such embodiments and features are possible and can result in preferred executions of the invention.

As used herein, wherein any variable, moiety, group, or the like occurs more than one time in any variable or structure, its definition at each occurrence is independent of its definition at every other occurrence. For example, each X of structure I is independently selected from -O-, -NH-, and -CH2-. Because the definition at each occurrence of X is independent of its definition at every other occurrence, the X of M may be -O- even though the X of Q is -NH-.

**Definition and Usage of Terms**

The following is a list of definitions for terms used herein:

As used herein “salt” is a cationic salt formed at any acidic (e.g., carboxyl) group, or an anionic salt formed at any basic (e.g., amino) group. Many such salts are known in the art. Preferred cationic salts include the alkali metal salts (such as, for example, sodium and potassium), alkaline earth metal salts (such as, for example, magnesium and calcium), and organic salts. Preferred anionic salts include the halides (such as, for example, chloride salts). Such acceptable salts must, when administered, be appropriate for mammalian use.

As used herein, “alkenyl” is an unsaturated straight or branched hydrocarbon chain radical. Alkenyls have at least one olefinic double bond. Alkenyls may be substituted or unsubstituted. Unless otherwise specified, alkenyls preferably have from 2 to about 8 carbon atoms (C₂ - C₈); preferably from 2 to about 10 carbon atoms (C₂ - C₁₀). Non-limiting examples of alkenyls include prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl, hex-2-enyl, hex-5-enyl, 2,3-dimethylbut-2-enyl, and the like.

As used herein, “aliphatic” includes both saturated and unsaturated straight, branched, cyclic (cycloaliphatic), or polycyclic (cycloaliphatic) aliphatic hydrocarbons. Unless otherwise specified, aliphatics have from 1 to about 15 carbon atoms, preferably from 1 to about 10 carbon atoms, more preferably from 1 to about 8 carbon atoms, most preferably from 1 to about 6 carbon atoms. Aliphatics are optionally substituted with one or more moieties selected from the
group consisting of hydroxy, alkoxy, acyl, carbamoyl, amino, alkylamino, dialkylamino, N-acylamino, keto, halo, trihalomethyl, cyano, carboxyl, alkyl, heteroalkyl, aryl, heteroaryl, heterocycloaliphatic, cycloaliphatic, and sulfonamido (unless otherwise specified, the alkyl, other aliphatic, alkoxy, and acyl substituent moieties preferably contain from 1 to 8, and in many cases from 1 to 6, contiguous aliphatic carbon atoms). Thus, as used herein, “aliphatic” is thus intended to include alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties.

As used herein, “alkyl” is a saturated straight or branched hydrocarbon chain radical. Alkyls may be substituted or unsubstituted. Unless otherwise specified, alkyls preferably have from 1 to about 8 carbon atoms (C₁ - C₈); preferably from 1 to about 6 carbon atoms (C₁ - C₆). Preferred alkyls include, for example, methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-pentyl, tert-pentyl, hexyl, iso-hexyl, and the like. Suitable substituted alkyls include, for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, and the like.

As used herein, “alkynyl” is an unsaturated straight or branched hydrocarbon chain radical. Alkynyls have at least one triple bond. Alkynyls may be substituted or unsubstituted. Unless otherwise specified, alkynyls preferably have from 2 to about 8 carbon atoms (C₂ - C₈); preferably from 2 to about 6 carbon atoms (C₂ - C₆). Non-limiting examples of alkynyls include prop-2-ynyl, but-2-enyl, but-3-ynyl, but-3-ynyl, pent-2-ynyl, 3-methylpent-4-ynyl, hex-2-ynyl, hex-5-ynyl, and the like.

As used herein, the terms “aryl” and “heteroaryl” are used to refer to mono- or polycyclic, heterocyclic, polycyclic, and polyheterocyclic unsaturated moieties having from 3 to 14 carbon atoms which may be substituted or unsubstituted. Non-limiting examples of useful aryl ring groups include, for example, phenyl, halophenyl, alkoxyphenyl, dialkoxyphenyl, trialkoxyphenyl, alkylenedioxyphenyl, naphthyl, phenanthryl, anthryl, phenanthro, and the like. Non-limiting examples of heteroaryl rings include 5-membered monocyclic ring groups such as thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, thiazolyl, and the like; 6-membered monocyclic groups such as pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, and the like, and polycyclic heterocyclic ring groups such as benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, indoliziny, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, pthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, benzothiazole, benzimidazole, tetrahydroquinoline cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, phenoxazinyl, and the like. The aryl
and heteroaryl moieties may be substituted with from one to five substituents selected from the
group consisting of hydroxy, C₁ - C₈ alkoxy, C₁ - C₈ alkyl, acyloxy, carbamoyl, amino, N-
acylamino, nitro, halo, trihalomethyl, cyano, and carboxy.

As used herein, "biohydrolyzable amides" are amides of the compounds used in the
present invention which do not interfere with the activity of the compound, or that are readily
converted in vivo by a mammalian subject to yield an active compound.

As used herein, "biohydrolyzable esters" are esters of the compounds used in the present
invention which do not interfere with the activity of the compound, or that are readily converted
in vivo by a mammalian subject to yield an active compound.

As used herein, "biohydrolyzable imides" are imides of the compounds used in the
present invention which do not interfere with the activity of the compound, or that are readily
converted in vivo by a mammalian subject to yield an active compound.

As used herein, "cycloaliphatic" refers to cyclic aliphatic groups preferably having from
three to seven (C₃ - C₇), more preferably three to six (C₃ - C₆) carbon atoms. Suitable
cycloaliphatics include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
cycloheptyl, and the like. Cycloaliphatics may be substituted or unsubstituted.

As used herein, "halo", "halogen", or the like refers to a fluoro, chloro, bromo, or iodo
substituent.

As used herein, "heteroaliphatic" refers to an aliphatic moiety which contains one or
more oxygen, sulfur, or nitrogen atoms, e.g., in place of one or more carbon atoms.
Heteroaliphatics may be substituted or unsubstituted.

As used herein, "heterocycloaliphatic" and "heterocycle" each refer to cyclic aliphatic
groups having one or more heteroatoms, and preferably three to seven ring atoms total including,
for example, oxetane, tetrahydrofuranyl, tetrahydropyranyl, aziridine, pyrrolidine, piperidine,
morpholine, piperazine, and the like. Heterocycloaliphatics (heterocycles) may be substituted or
unsubstituted.

As used herein, "pharmaceutically acceptable" means suitable for use in a human or
other mammal, preferably human.

As used herein, "safe and effective amount of a compound" (or composition, or the like)
means an amount that is effective to exhibit biological activity, preferably wherein the biological
activity is arresting and / or reversing hair loss or promoting hair growth, at the site(s) of activity
in a mammalian subject, without undue adverse side effects (such as toxicity, irritation, or
allergic response), commensurate with a reasonable benefit/risk ratio when used in the manner of this invention.

As used herein, moieties may be substituted or unsubstituted. Unless otherwise specified, preferred substituents include hydroxy, alkoxy, acyl, carbamoyl, amino, alkylamino, dialkylamino, N-acylamino, keto, halo, trihalomethyl, cyano, carboxyl, alkyl, heteroalkyl, aryl, heteroaryl, heterocycloaliphatic, cycloaliphatic, and sulfonamido (unless otherwise specified, the alkyl, other aliphatic, alkoxy, and acyl preferably contain from 1 to about 8, more preferably from 1 to about 6, contiguous aliphatic carbon atoms).

**Methods and Compounds of the Present Invention**

The present invention relates to methods of treating hair loss comprising administering a composition comprising a compound having the structure:

\[
M\text{-}L\text{-}Q
\]

and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein M and Q are each, independently, radicals of structure I and wherein L is a linker moiety which covalently links M and Q together. Preferably, M and Q are equivalent.

As used herein, structure I is:

![Chemical Structure](image)

wherein:

(a) each G is, independently, selected from nil, aliphatic, heteroaliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, and

(b) each n is, independently, an integer selected from 1 and 2;

(c) each X is, independently, selected from -O-, -NH-, and -CH₂-;

(d) each R₁ is, independently, selected from aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aryl, and heteroaryl;
(e) each $C_A$ is a carbon atom;

(f) each $C_B$ is a carbon atom;

(g) each $B_1$ and $B_2$ is, independently, selected from hydrogen, aliphatic, heteroaliphatic, aryl, and heteroaryl; or wherein each $B_1$ and $B_2$ of the same $G$ are, together, a carbonyl group; and

(h) each $R_2$ is, independently, selected from nil, aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aryl, and heteroaryl;

wherein when $G$ of $M$ is nil, $L$ is covalently attached to $C_A$ of $M$; wherein when $G$ of $Q$ is nil, $L$ is covalently attached to $C_A$ of $Q$; wherein when $B_1$ and $B_2$ of $M$ are, together, a carbonyl group and $R_2$ is nil, $L$ is covalently attached to $C_B$ of $M$; and wherein when $B_1$ and $B_2$ of $Q$ are, together, a carbonyl group and $R_2$ is nil, $L$ is covalently attached to $C_B$ of $Q$.

The Linker $L$

The present compounds are "divalent" meaning they have two groups, $M$ and $Q$, which can potentially bind with a receptor binding site. The linker, $L$, of these compounds covalently connects $M$ to $Q$. The linker may be any mechanism through which $M$ and $Q$ may be covalently bonded together. The linker may, but need not, participate in binding which a receptor binding site. However, a preferred linker will optimize, e.g., physiochemical and/or pharmacokinetic properties of the compound.

Because the linker is a mechanism for covalent bonding, the ordinarily skilled artisan will recognize that the linker may be selected from a broad range of structures. A simple, and preferred, linker is merely a covalent bond which links $M$ to $Q$, herein referred to as "bond". Another preferred linker is a heteroatom diradical e.g., -O- or -N(OH)-. Preferred heteroatom radicals are selected from oxygen (-O-), nitrogen (-NH- or substituted -N-), and sulfur (-S-); more preferably oxygen and nitrogen; and most preferably oxygen. Wherein nitrogen is the linker, it may be substituted (substituted -N-) wherein the preferred substituent is alkyl.

Particularly preferred linkers include ethers, thioethers, amines, amides, ureas, carbamates, sulfonamides, thiocarbamates, esters, thioesters, and ketones.

Other non-limiting examples of linkers include radicals such as, for example, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, and heteroarylalkynyl. These radicals may be substituted or unsubstituted. Preferred among these examples are alkyl, alkenyl, heteroalkyl, heteroalkenyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, and heteroarylalkenyl. More preferred among these examples are alkyl, heteroalkyl, aryl, arylalkyl,
heteroaryl, and heteroaryalkyl, most preferably aryl. Most preferred among these examples are phenyl, naphthyl, and biphenyl.

In a preferred embodiment of the invention, the linker is a bis-amide linker, a retro bis-amide linker, a polyether urea linker, or a polyether linker. These linkers are described below. The “attachment locations” are the points at which M and Q, respectively, are linked to L.

Overall, the most preferred linkers are selected from bond, aryl, alkyl, biaryl ether (i.e., aryl-O-aryl), biaryl methyl (i.e., aryl-CH₂-aryl), -O-, -S-, and -NH-, more preferably bond, lower alkyl, aryl, biaryl ether, -O-, and-NH-, even more preferably bond, aryl, biaryl ether, and -O-, with the most preferable among these being phenyl, naphthyl, biphenyl, biphenyl ether, biphenyl methyl, methyl, and -O-. Examples of bis-amide linkers are:
Examples of retro bis-amide linkers are:
An example of a polyether urea linker is:

Examples of polyether linkers are:
A preferred sulfonamide linker is shown below:

The G Moiety

The G moiety is present in structure I as described above. Each G is independently selected from nil, aliphatic, heteroaliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, and

\[
\begin{align*}
\text{B}_1 & \text{C}_B \\
\text{B}_2 & \text{R}_2
\end{align*}
\]

Preferably, each G is independently selected from aliphatic, heteroaliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, and

\[
\begin{align*}
\text{B}_1 & \text{C}_B \\
\text{B}_2 & \text{R}_2
\end{align*}
\]

wherein each B₁ and B₂ of the same G are, together, a carbonyl group.

More preferably, each G is independently selected from aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, and

\[
\begin{align*}
\text{B}_1 & \text{C}_B \\
\text{B}_2 & \text{R}_2
\end{align*}
\]

wherein each B₁ and B₂ of the same G are, together, a carbonyl group.
Wherein G requires an R₂ moiety, each R₂ is independently selected from nil, aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aryl, and heteroaryl. Preferably, each R₂ is independently selected from nil, aliphatic, heterocycloaliphatic, aryl, and heteroaryl. More preferably, each R₂ is independently selected from nil, aliphatic, aryl, and heteroaryl. Most preferably, each R₂ is independently selected from nil, aliphatic (preferably branched alkyl) and aryl.

Wherein G requires B₁ and/or B₂ moieties, each B₁ and B₂ is independently selected from hydrogen, aliphatic, heteroaliphatic, aryl, and heteroaryl; or wherein each B₁ and B₂ of the same G are, together, a carbonyl group. Preferably, each B₁ and B₂ is independently selected from hydrogen and aliphatic (preferably, alkyl); or wherein each B₁ and B₂ of the same G are, together, a carbonyl group. Most preferably, each B₁ and B₂ is hydrogen or wherein each B₁ and B₂ of same G are, together, a carbonyl group.

Wherein the G moiety of M or Q is nil, then the linker is preferably selected from alkyl, heteroalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, most preferably aryl. Wherein when G of M is nil, L is covalently attached to Cₐ of M. Wherein when G of Q is nil, L is covalently attached to Cₐ of Q.

Wherein the R₂ moiety of M or Q is nil, then the linker is preferably selected from alkyl, heteroalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, most preferably aryl. Wherein when R₂ of a G moiety is nil, then the linker moiety (L) is directly attached to Cₐ of that same G moiety.

The Integer n

Each integer n is, independently, and integer selected from 1 and 2. Preferably, at least one integer n is 2. Most preferably, each integer n is 2.

The X Moiety

Each X is independently selected from -O-, -NH-, and -CH₂-. Preferably, each X is independently selected from -O- and -NH-. More preferably, at least one X is -NH-. Most preferably, each X is -NH-.

The R₁ Moiety

Each R₁ moiety is, independently, selected from aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aryl, and heteroaryl. Most preferably, each R₁ moiety is aliphatic (preferably alkyl) substituted with at least one of alkyl, heteroalkyl, heterocycle, aryl, and heteroaryl. For example, a preferred R₁ moiety is:
wherein:

(a) each $R_4$ is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl, and heteroaryl;

(b) each $R_5$ is $C_1 - C_4$ alkyl; and

(c) each $R_6$ is selected from the group consisting of alkyl, heteroalkyl, heterocycle, aryl, and heteroaryl.

Preferably, in this $R_i$ moiety, $R_5$ is $C_1$ alkyl (preferably methyne) and each of $R_4$ and $R_6$ are alkyl (most preferably, $C_3$ alkyl), wherein each $R_4$ and $R_6$ are preferably independently substituted with aryl (most preferably, substituted or unsubstituted phenyl).

Preferred compounds useful in the methods of the present invention are shown in Table 1 below:

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td><img src="image" alt="Chemical Structures" /></td>
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<tr>
<td><img src="image" alt="Chemical Structures" /></td>
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</tbody>
</table>
In the following compounds, $R_3$ of $M$ is methyne, $R_4$ of $M$ is heteroalkyl substituted with aryl, $R_6$ of $M$ is heteroalkyl substituted with oxo, $R_5$ of $Q$ is methyne, $R_4$ of $Q$ is heteroalkyl substituted with aryl, $R_6$ of $Q$ is heteroalkyl substituted with oxo, and $L$ is phenyl:

**Table 2**
Preferred Compounds of the Present Invention

Preferred compounds of the present invention which may be utilized in the present methods have the structure:

\[ \text{M-L-Q} \]

and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein M and Q are each, independently, radicals of structure II and wherein L is a linker moiety which covalently links M and Q together; and wherein structure II is:

\[
\begin{array}{c}
\text{G} \\
\text{C}_A=\text{O} \\
\text{N} \\
\text{X} \\
\text{R}_1
\end{array}
\]

wherein:

(a) each G is independently selected from nil and

\[
\begin{array}{c}
\text{O} \\
\text{C}_B
\end{array}
\]

(b) each n is, independently, an integer selected from 1 and 2;

(c) each X is independently selected from -O-, -NH-, and -CH2-;

(d) each R1 is, independently, selected from aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aryl, and heteroaryl;

(e) each C_A is a carbon atom;

(f) each C_B is a carbon atom;

(g) L is aryl;

wherein when G of M is nil, L is covalently attached to C_A of M; wherein when G of Q is nil, L is covalently attached to C_A of Q; wherein when G of M is:

\[
\begin{array}{c}
\text{O} \\
\text{C}_B
\end{array}
\]

L is covalently attached to C_B of M; and wherein when G of Q is:

\[
\begin{array}{c}
\text{O} \\
\text{C}_B
\end{array}
\]

L is covalently attached to C_B of Q.
Other preferred compounds of the present invention which may be utilized in the present methods have the structure:

\[ \text{M-L-Q} \]

and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein M and Q are each, independently, radicals of structure III and wherein L is a linker moiety which covalently links M and Q together, wherein structure III is:

\[
\begin{array}{c}
\text{G} \\
\text{B}_1 \\
\text{B}_2 \\
\text{R}_2
\end{array}
\]

wherein:

(a) each G is independently selected from aliphatic, heteroaliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, and

(b) each \( n \) is, independently, an integer selected from 1 and 2;
(c) each X is independently selected from \(-\text{O}-\), \(-\text{NH}-\), and \(-\text{CH}_2-\);
(d) each \( \text{B}_1 \) and \( \text{B}_2 \) is, independently, selected from hydrogen, aliphatic, heteroaliphatic, aryl, and heteroaryl; or wherein each \( \text{B}_1 \) and \( \text{B}_2 \) of the same G are, together, a carbonyl group;
(e) each \( \text{R}_1 \) is, independently, selected from aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aryl, and heteroaryl;
(f) each \( \text{R}_2 \) is, independently, selected from aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aryl, and heteroaryl; and
(g) L is selected from bond, \(-\text{O}-\), \(-\text{S}-\), and \(-\text{NH}-\).

Highly preferred compounds wherein M and Q are each structures II or III (each of these are also compounds wherein M and Q are contemplated within structure I) are shown below.

In the following compound, G of M is phenyl, G of Q is phenyl, and the linker is \(-\text{O}-\):
In the following compound, \( B_1 \) and \( B_2 \) of \( M \) are, together, carbonyl, and \( R_2 \) of \( M \) is phenyl, \( B_1 \) and \( B_2 \) of \( Q \) are, together, carbonyl, and \( R_2 \) of \( Q \) is phenyl, and \( L \) is \(-\text{O-}\):

In the following compound, \( G \) of \( M \) is nil, \( G \) of \( Q \) is nil, and \( L \) is biphenyl, linked directly to \( C_A \) of \( M \) and \( C_A \) of \( Q \):

In the following compound, \( B_1 \) and \( B_2 \) of \( M \) are, together, carbonyl, and \( R_2 \) of \( M \) is nil, \( B_1 \) and \( B_2 \) of \( Q \) are, together, carbonyl, \( R_2 \) of \( Q \) is nil, and \( L \) is biphenyl, linked directly to \( C_A \) of \( M \) and \( C_A \) of \( Q \):
In the following compound, G of M is nil, G of Q is nil, and L is naphthyl, linked directly to C\textsubscript{A} of M and C\textsubscript{A} of Q:

![Chemical structure 1]

In the following compound, B\textsubscript{1} and B\textsubscript{2} of M are, together, carbonyl, and R\textsubscript{2} of M is nil, B\textsubscript{1} and B\textsubscript{2} of Q are, together, carbonyl, R\textsubscript{2} of Q is nil, and L is naphthyl, linked directly to C\textsubscript{A} of M and C\textsubscript{A} of Q:

![Chemical structure 2]

**Analytical Methods**

The present invention relates to methods of treating hair loss by administering a compound having a structure as described herein. Of such compounds, the preferred compounds are non-immunosuppressive. Compounds (test compounds) may be tested for their ability to induce anagen and their immunosuppressive activity (or lack thereof) using the following methods. Alternatively, other methods well-known in the art may be used (but with the term "non-immunosuppressive" being defined according to the method disclosed herein below).

**Telogen Conversion Assay:**

25
The Telogen Conversion Assay measures the potential of a test compound to convert mice in the resting stage of the hair growth cycle ("telogen"), to the growth stage of the hair growth cycle ("anagen").

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, IN) 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 a hair growth promoter is applied. The Telogen Conversion Assay herein below is used to screen compounds for potential hair growth by measuring melanogenesis.

Three groups of 44 day-old C3H mice are utilized: a vehicle control group, a positive control group, and a test compound group, wherein the test compound group is administered a compound used in the method of the present invention. The length of the assay is at least 19 days with 15 treatment days (wherein the treatment days occur Mondays through Fridays). Day 1 is the first day of treatment. Most studies will end on Day 19, but a few may be carried out to Day 24 if the melanogenesis response looks positive, but occurs slowly. A typical study design is shown in Table 3 below:

<table>
<thead>
<tr>
<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>1</td>
<td>1 - 10</td>
<td>Test Compound</td>
<td>5% in vehicle**</td>
<td>400 µL topical</td>
<td>19 or 24 days</td>
</tr>
<tr>
<td>2</td>
<td>11 - 20</td>
<td>Cyclosporin A</td>
<td>0.19% in vehicle**</td>
<td>400 µL topical</td>
<td>19 or 24 days</td>
</tr>
<tr>
<td>3</td>
<td>21 - 30</td>
<td>Vehicle**</td>
<td>N/A</td>
<td>400 µL topical</td>
<td>19 or 24 days</td>
</tr>
</tbody>
</table>

**The vehicle is 60% ethanol, 20% propylene glycol, and 20% dimethyl isosorbide (commercially available from Sigma Chemical Co., St. Louis, MO).

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 reach the skin.
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 the mice convert from telogen to anagen their skin color will become more bluish-black. As indicated in Table 4, the grades 0 to 4 represent the following visual observations as the skin progresses from white to bluish-black:

<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 (indication 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</td>
<td>4</td>
</tr>
<tr>
<td>(indication of mouse in full anagen)</td>
<td></td>
</tr>
</tbody>
</table>

**Immunosuppression Assay:**

The immunosuppression assay herein predicts the immunosuppressive activity of a compound used in the method of the present invention. The assay is performed as follows:

Spleens are excised from euthanized (CO₂ asphyxiation) adult male C3H mice ranging in age from seven to sixteen weeks old (live mice commercially available from Harlan Sprague Dawley, Inc., Indianapolis, IN). The spleens are placed immediately in cold Hanks Balanced Salt Solution (HBSS, commercially available from Gibco-BRL, Gaithersburg, MD). The spleens are then ground up between frosted glass slides and filtered through a sterile screen to remove tissue debris. The resulting cell suspension is underlaid with an equal volume of Ficoll-Paque Plus (commercially available from Pharmacia Biotech, Piscataway, NJ) and centrifuged at 400 x g for approximately forty minutes at 20 °C in order to collect the splenocytes. The splenocytes are collected from the interface using a disposable pipet and are washed twice with HBSS, followed by centrifugation at 100 x g for ten min at 20 °C. Splenocytes are resuspended in five to ten mL of cell culture media consisting of phenol red-free RPMI 1640 (culture media commercially available from Gibco-BRL) containing 10% heat-inactivated fetal bovine serum (Gibco-BRL), penicillin (50 U/mL), streptomycin (100 µg/mL), L-glutamine (2 mM), 2-mercaptoethanol (10⁻⁵ M), and N-2-hydroxyethylpiperazine-N'-2-
ethanesulfonic acid (HEPES) (10 mM). The cells are counted and checked for viability using, for example, trypan blue. Splenocytes are resuspended in medium at 10⁵ cells/mL and pipetted into 96 well round bottom plates at 10⁵ cells/well. Splenocytes are activated by addition of 50 μL/well of concanavalin A (final assay concentration = 5 μg/ml) in the presence or absence of a test compound. Test compounds are made up as stock solutions in methyl sulfoxide (DMSO), then diluted in medium and 50 μL/well added, such that the final concentration of DMSO in the assay is below 0.05%. The plates are incubated at 37 °C with 5% CO₂ for 48 hours. After 48 hours, the cells are pulsed with 1 μCi/well of methyl-³H-thymidine (commercially available from Amersham, Buckinghamshire, England) and incubated an additional 24 hours.

After 24 hours, the cells are harvested onto GF/C filter plates (commercially available from Packard, Downers Grove, IL), solubilized in Microscint 20 (Packard), and counted on a TopCount microplate scintillation and luminescence plate counter (Packard). Activity is measured as a percentage of control activity in the absence of test compound and plotted versus test compound concentration. The data are fit to a 4-parameter curve fit (Sigmplot) and IC₅₀ values are calculated. As used herein, test compounds are considered non-immunosuppressive if, by using this method, the ratio of (cyclosporin A IC₅₀/test compound IC₅₀) x 100 is less than or equal to 0.02, i.e., a non-immunosuppressive test compound has ≤ 2% of the immunosuppressive activity of cyclosporin A.

Cell viability is assessed using the MTT (3-[4,5-dimethyl-thiazolyl-2-yl]2,5-diphenyl-tetrazolium bromide) dye assay as described by Nelson et al., Journal of Immunology, Vol. 150, No. 6, pp. 2139 - 2147 (1993), with the exception that the assay is carried out in serum-free, phenol red-free RPMI 1640 and the dye is solubilized in 100 μL/well DMSO and read at an OD of 540 nm with a background correction at 650 nm on a SpectraMax Plus microplate reader (Molecular Devices, Menlo Park, CA).

Multi-Drug Resistance

As disclosed herein, the present compounds are also useful, for example, to increase the antiproliferative activity of a drug and / or prevent and / or treat multi-drug resistance. The present compounds may be assayed for this property as described in U.S. Patent No. 5,744,485, Zelle et al., assigned to Vertex Pharmaceuticals Inc., issued April 28, 1998, U.S. Patent No. 5,726,184, Zelle et al., assigned to Vertex Pharmaceuticals Inc., issued March 10, 1998, U.S. Patent No. 5,620,971, Armistead et al., assigned to Vertex Pharmaceuticals Inc., issued April 15,

Methods of Making

The compounds used in the methods of the present invention are prepared according to methods which are well-known to those skilled in the art. The starting materials used in preparing the compounds are known, made by known methods, or are commercially available as a starting material.

It is recognized that the skilled artisan in the art of organic chemistry can readily carry out standard manipulations of organic compounds without further direction. Examples of such manipulations are discussed in standard texts such as J. March, Advanced Organic Chemistry, John Wiley & Sons, 1992.

The skilled artisan will readily appreciate that certain reactions are best carried out when other functionalities are masked or protected in the compound, thus increasing the yield of the reaction and/or avoiding any undesirable side reactions. Often, the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many such manipulations can be found in, for example, T. Greene, Protecting Groups in Organic Synthesis, John Wiley & Sons, 1981.

The compounds of the present invention may have one or more chiral center. As a result, one may selectively prepare one optical isomer, including diastereomers and enantiomers, over another, for example by chiral starting materials, catalysts or solvents, or may prepare both stereoisomers or both optical isomers, including diastereomers and enantiomers at once (a racemic mixture). Since the compounds of the invention may exist as racemic mixtures, mixtures of optical isomers, including diastereomers and enantiomers, or stereoisomers may be separated using known methods, such as through the use of, for example, chiral salts and chiral chromatography.

In addition, it is recognized that one optical isomer, including a diastereomer and enantiomer, or a stereoisomer, may have favorable properties over the other. Thus, when disclosing and claiming the invention, when one racemic mixture is disclosed, it is clearly contemplated that both optical isomers, including diastereomers and enantiomers, or stereoisomers substantially free of the other are disclosed and claimed as well.

The syntheses of compounds utilized in methods of the present invention are described in the following references: Keenan et al., "Synthesis and Activity of Bivalent FKBP12 Ligands

In addition, the following provides non-limiting examples illustrating more specifically the methods of making various compounds of the present invention.

As used herein, the following abbreviations are used:

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (commercially available from Fluka Chemical, Switzerland)</td>
<td>PyBOP</td>
</tr>
<tr>
<td>trifluoroacetic acid</td>
<td>TFA</td>
</tr>
<tr>
<td>triethylamine</td>
<td>TEA</td>
</tr>
<tr>
<td>4-dimethylaminopyridine</td>
<td>4-DMAP</td>
</tr>
<tr>
<td>N,N - dimethylformamide</td>
<td>DMF</td>
</tr>
<tr>
<td>N,N - diisopropylethylamine</td>
<td>i-Pr₂NEt or i-Pr₂EtN</td>
</tr>
</tbody>
</table>

**Example 1**

![Chemical structure](image)

1a. **(S)-(N-tert-Butoxycarbonyl)pipecolinic acid 1,7-diphenyl-4-heptylamide**: (S)-(N-tert-Butoxycarbonyl)pipecolinic acid (4.66 g, 20.3 mmol) is dissolved in 200 mL of DMF. 1,7-Diphenyl-4-aminoheptane (5.44 g, 20.3 mmol) and i-Pr₂EtN (5.25 g, 40.7 mmol) are added followed by PyBOP (10.6 g, 20.3 mmol). The reaction is stirred for 18 hours at room temperature, then poured onto ice-cold 0.1N HCl (800 mL) and extracted with ethyl acetate (800 mL). The layers are separated and the organic layer washed successively with brine (200 mL), saturated NaHCO₃ solution (400 mL) and brine (200 mL). The organic solution is dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the product by chromatography on silica gel affords the desired amide 1a.
1b. (S)-Pipolic acid 1,7-diphenyl-4-heptylamide: The amide 1a (8.74 g, 18.3 mmol) is dissolved in 150 mL of anhydrous dichloromethane. TFA (100 mL) is added dropwise over a 5 minute period. After about 2 hours the mixture is cooled in an ice-bath and saturated K₂CO₃ solution is added until the pH is approximately 8. The mixture is transferred to a separatory funnel containing dichloromethane (200 mL) and water (200 mL) and shaken. The organic layer is separated and washed with water (200 mL) before drying over MgSO₄. The mixture is filtered and concentrated under reduced pressure to afford the desired amine 1b.

Example 2

2. Bis-4,4’-((S)-N-(phenylcarbonyl)pipolic acid 1,7-diphenyl-4-heptylamide) ether: The amine of Example 1b (8.43 g, 22.3 mmol), 4,4’-oxybis(benzoic acid) (2.5 g, 9.7 mmol; Aldrich Chemical Co., Milwaukee, WI) and i-Pr₂EtN (8.4 mL, 48.4 mmol) are dissolved in 150 mL of anhydrous dichloromethane. The PyBOP (12.6 g, 24.2 mmol) is added in one portion. The reaction is stirred for 6 hours at room temperature, then poured onto ice-cold 0.1N HCl (300 mL) and extracted with dichloromethane (300 mL). The layers are separated and the organic layer washed successively with saturated NaHCO₃ solution (150 mL) and brine (50 mL). The organic solution is dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the product by chromatography on silica gel affords the desired amide 2.
3. 2,6-Naphthalenedicarbonyl((S)-N-pipecolic acid 1,7-diphenyl-4-heptylamine): The amine of Example 1b (8.43 g, 22.3 mmol), 2,6-naphthalenedicarboxylic acid (2.1 g, 9.7 mmol; Aldrich Chemical Co, Milwaukee, WI) and i-Pr₂EtN (8.4 mL, 48.4 mmol) are dissolved in 200 mL of anhydrous dichloromethane. The PyBOP (12.6 g, 24.2 mmol) is added in one portion. The reaction is stirred for about 22 hours at room temperature, then poured onto ice-cold 0.1N HCl (400 mL) and extracted with dichloromethane (300 mL). The layers are separated and the organic layer washed successively with saturated NaHCO₃ solution (150 mL) and brine (50 mL). The organic solution is dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the product by chromatography on silica gel affords the desired amide 3.

Example 4

4a. 4,4'-biphenylglyoxylic acid: 4,4'-diacetylbi phenyl (5 g, 21 mmol, Aldrich Chemical Co., Milwaukee, WI) is dissolved in anhydrous pyridine (65 mL) at ambient temperature. Selenium dioxide (9.3 g, 83.9 mmol) is added in one portion and the resulting mixture is carefully heated to reflux. After 24 hours at reflux the reaction mixture is cooled to ambient temperature then filtered through a pad of diatomaceous earth, washed with pyridine, and concentrated under
reduced pressure. The residue is slurried in ethyl acetate (100 mL) and 1 N HCl (100 mL) until dissolution is complete. The layers are separated, and the aqueous layer is extracted with ethyl acetate (100 mL). The combined ethyl acetate extracts are dried (MgSO₄), filtered, and concentrated under vacuum to afford the desired bis-α-ketoacid 4a.

4b. 4,4’-biphenylglyoxylic acid (S)-N-pepcolic acid 1,7-diphenyl-4-heptylamide: Amine 1b (7.3 g, 19.3 mmol) is dissolved in anhydrous dichloromethane (75 mL) at ambient temperature. 4,4’-biphenyl-glyoxylic acid 4a (2.5 g, 8.4 mmol) is added followed by i-Pr₃EtN (7.3 mL, 42 mmol) and PyBOP (10.91 g, 21 mmol) in succession. The reaction solution is stirred at ambient temperature for 18 hours then concentrated under vacuum. The residue is dissolved in ethyl acetate (250 mL) then washed successively with 0.2 N HCl (100 mL), saturated aqueous sodium bicarbonate (50 mL), and brine (50 mL). The organic solution is dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the product by preparative chromatography affords the desired bis-α-ketoamide 4b.
Example 5

5a. 4,4’-(phenylglyoxylic acid) ether: 4-acetylphenyl ether (5 g, 19.2 mmol, Trans World Chemicals, Rockville, MD) is dissolved in anhydrous pyridine (65 mL) at ambient temperature. Selenium dioxide (8.73 g, 78.7 mmol) is added in one portion and the resulting mixture is carefully heated to reflux. After 24 hours at reflux the reaction mixture is cooled to ambient temperature then filtered through a pad of diatomaceous earth, washed with pyridine, and concentrated under reduced pressure. The residue is dissolved in ethyl acetate (250 mL) and extracted successively with 1 N HCl (100 mL), then saturated aqueous sodium bicarbonate (2 x 50 mL). The combined aqueous bicarbonate extracts are acidified with concentrated HCl then extracted with dichloromethane (3 x 50 mL). A precipitate persists throughout the dichloromethane extractions which is removed by filtration, water washed, and dried to afford the desired bis-α-ketoacid 5a.
5b. 4,4'-[(phenylglyoxy] ether((S)-N-pipecolic acid 1,7-diphenyl-4-heptylamide): Amine 1b (7.3 g, 19.3 mmol) is dissolved in anhydrous dichloromethane (75 mL) at ambient temperature. 4,4'-biphenyl-glyoxylic acid 5a (2.63 g, 8.37 mmol) is added followed by i-Pr$_3$EtN (7.3 mL, 42 mmol), DMF (25 mL), and PyBOP (10.9 g, 21 mmol) in succession. The reaction slurry is stirred at ambient temperature for 5 hours then additional PyBOP (5 g, 9.61 mmol) is added. The slurry is stirred at ambient temperature for another 13 hours then filtered to remove insoluble materials. The filtrate is concentrated under reduced pressure. The residue is dissolved in ethyl acetate (250 mL) then washed successively with a mixture of water (75 mL) and brine (25 mL), 0.2 N HCl (100 mL), saturated aqueous sodium bicarbonate (75 mL), and brine (50 mL). The organic solution is concentrated under reduced pressure. Purification of the product by preparative chromatography affords the desired bis-α-ketoamide 5b.

Use of the Present Compounds

The methods of the present invention is performed by administration of a compound having a structure herein and a pharmaceutically-acceptable carrier.

The compounds herein may be used for the treatment of such conditions as treating hair loss in mammals, including arresting and/or reversing hair loss and promoting hair growth. Such conditions may manifest themselves in, for example, alopecia, including male pattern baldness and female pattern baldness.

While certain of the present compounds may exhibit immunosuppressive activity, the preferred compounds of the present invention are, as defined herein, non-immunosuppressive.

Furthermore, in addition to treating hair loss, the compounds utilized in the present invention may be used to treat a variety of clinical conditions which include, but are not limited to, multi-drug resistance (particularly for use in cancer chemotherapy), neurological disorders and neurodegenerative diseases, cardiac injury associated with ischemia/reperfusion injury, and treatment of fungal, microbial, viral (especially HIV), malarial or other parasitic diseases or conditions. The present compounds may also be useful as inhibitors of multi-drug transporter proteins to enhance, for example, pharmacokinetics and bioavailability. Certain compounds of the present invention may exhibit immunomodulatory properties. These compounds would prove useful in the treatment of organ transplant rejection and various autoimmune diseases which include, but are not limited to, Behcet’s disease, Crohn’s disease, systemic lupus erythematosus, psoriasis, rheumatoid arthritis, eczema, multiple sclerosis, myasthenia gravis, insulin-dependent diabetes mellitus, and Graves’ disease. In addition, the present compounds
may have utility for the treatment of certain inflammatory and allergic disease states, including urticaria, allergic contact dermatitis, atopic dermatitis, atopic keratoconjunctivitis, inflammatory bowel disease, and asthma. The present compounds may also be useful in the treatment of cardiac hypertrophy in congestive heart failure.

The present compounds may also be useful in combination with a matrix metalloproteinase inhibitor for treatment of various conditions including, for example, tissue destructive diseases mediated by excessive metalloproteinase activity, cancer, and multi-drug resistance, as well as all of the conditions previously mentioned herein above. Particularly preferred matrix metalloproteinase inhibitors useful in such combination include those described in U.S. Patent No. 5,830,915, Pikul et al., assigned to The Procter & Gamble Co., filed August 26, 1997; U.S. Patent Application Serial No. 08/918,317, Natchus et al., assigned to The Procter & Gamble Co., filed August 26, 1997; U.S. Patent Application Serial No. 08/918,957, Pikul et al., assigned to The Procter & Gamble Co., filed August 26, 1997; U.S. Patent Application Serial No. 08/918,419, Pikul et al., assigned to The Procter & Gamble Co., filed August 26, 1997; U.S. Patent Application Serial No. 08/921,953, De et al., assigned to The Procter & Gamble Co., filed August 28, 1996; and U.S. Patent Application Serial No. 08/918,328, Wang et al., assigned to The Procter & Gamble Co., filed August 26, 1997.

Preferably, in the methods of the present invention, the compounds are formulated into pharmaceutical compositions for use in treatment or prophylaxis of conditions such as the foregoing. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington’s Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. (1990).

Typically, from about 5 mg to about 3000 mg, more preferably from about 5 mg to about 1000 mg, more preferably from about 10 mg to about 100 mg, of a compound having a structure as described herein is administered per day for systemic administration. It is understood that these dosage ranges are by way of example only, and that daily administration can be adjusted depending on various factors. The specific dosage of the compound 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 compound 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.
According to the present invention, the subject compounds are co-administered with a pharmaceutically-acceptable carrier ("carrier"). The term pharmaceutically-acceptable carrier, as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with a compound of the present invention, 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, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal, preferably mammal, being treated. The carrier can itself be inert or it can possess pharmaceutical benefits of its own.

The compositions utilized in this invention may be in any of a variety of forms, suitable (for example) for oral, rectal, topical, nasal, ocular or parenteral administration. Of these, topical or oral administration is especially preferred. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. These include solid or liquid fillers, diluents, hydrodriptops, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the activity of the compound of the present invention. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material 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 Pharmaceutics, 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).

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENs; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents;
tabletting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered.

In particular, pharmaceutically-acceptable carriers for systemic administration include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the pharmaceutically-acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight of the total composition.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50%, of a compound of the present invention. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for oral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules (including time release and sustained release formulations) typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like
taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be readily made by a person skilled in the art.

Orally administered compositions also include liquid solutions, emulsions, suspensions, powders, granules, elixirs, tinctures, syrups, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

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 sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

The compounds of the present invention may also be topically administered. The carrier of the topical composition preferably aids penetration of the present compounds into the skin to reach the environment of the hair follicle. Topical compositions of the present invention may be in any form including, for example, solutions, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like.

Topical compositions containing the active compound can be admixed with a variety of carrier materials well known in the art, such as, for example, water, alcohols, aloe vera gel,
allantoin, glycerine, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, and the like.

Other materials suitable for use in topical carriers include, for example, emollients, solvents, humectants, thickeners and powders. Examples of each of these types of materials, which can be used singly or as mixtures of one or more materials, are as follows:

Emollients, such as stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, iso-propyl isostearate, stearic acid, iso-butyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-n-butyl sebacate, iso-propyl myristate, iso-propyl palmitate, iso-propyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, and myristyl myristate; propellants, such as propane, butane, iso-butane, dimethyl ether, carbon dioxide, and nitrous oxide; solvents, such as ethyl alcohol, methylene chloride, iso-propanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monooethyl ether, dimethyl sulfoxide, dimethyl formamide, tetrahydrofuran; humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, and gelatin; and powders, such as chalk, talc, fuller’s 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, and ethylene glycol monostearate.

The compounds used in the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines. A preferred formulation for topical delivery of the present compounds utilizes liposomes such as described in Dowton et al., “Influence of Liposomal Composition on Topical Delivery of Encapsulated Cyclosporin A: I. An in vitro Study Using Hairless Mouse Skin”, S.T.P. Pharma Sciences, Vol. 3, pp. 404 - 407 (1993), Wallach and Philippot, “New Type of Lipid Vesicle: Novasome™”, Liposome Technology, Vol. 1, pp. 141 - 156 (1993), and Wallach, U.S. Patent No. 4,911,928, assigned to Micro-Pak, Inc., issued March 27, 1990.

The compositions utilized in the present invention may also optionally comprise an activity enhancer. The activity enhancer can be chosen from a wide variety of molecules which can function in different ways to enhance hair growth effects of a compound of the present invention. Particular classes of activity enhancers include other hair growth stimulants and penetration enhancers.

Additional hair growth stimulants can be chosen from a wide variety of molecules which can function in different ways to enhance the hair growth effects of the compositions and methods of the present invention. These optional other hair growth stimulants, when present, are typically employed in the compositions herein at a level ranging from about 0.01% to about
15%, preferably from about 0.1% to about 10%, most preferably from about 0.5% to about 5% by weight of the composition.


One suitable class of additional hair growth stimulant for use herein are antiandrogens. Examples of suitable antiandrogens may include, but are not limited 5-α-reductase inhibitors such as finasteride and those described in U.S. Patent 5,516,779, issued May 14, 1996 (herein incorporated by reference) 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. Patent 5,480,913, issued January 2, 1996, flutamide, and those described in U.S. Patents 5,411,981, issued May 2, 1995, U.S. Patent 5,565,467, issued October 15, 1996 and U.S. Patent 4,910,226, issued March 20, 1990, all of which are herein incorporated by reference.

Another suitable class of optional hair growth stimulants are antimicrobials such as selenium sulfide, ketoconazole, triclocarban, triclosan, zinc pyrithione, itraconazole, asiatic acid, hinokitiol, mipirocin and those described in EPA 0,680,745 (herein incorporated by reference), clinacycin hydrochloride, benzoyl peroxide, benzyl peroxide and minocyclin.

Anti-inflammatories can also be incorporated into the compositions herein as an optional hair growth stimulant. Examples of suitable anti-inflammatories may include glucocorticoids such as hydrocortisone, mometasone furoate and prednisolone, nonsteroidal anti-inflammatories including cyclooxygenase or lipoxygenase inhibitors such as those described in U.S. Patent 5,756,092, and benzydamine, salicylic acid, and those compounds described in EPA 0,770,399, published May 2, 1997, WO 94/06434, published March 31, 1994, and FR 2,268,523, published November 21, 1975, all of which are herein incorporated by reference.


Prostaglandin agonists or antagonists can also be used as optional hair growth stimulants in the compositions herein. Examples of suitable prostaglandins agonists or antagonists include latanoprost and those described in WO 98/33497, Johnstone, published August 6, 1998, WO 95/11003, Stjernschantz, published April 27, 1995, JP 97-100091, Ueno and JP 96-134242, Nakamura.

Another class of optional hair growth stimulants for use herein are retinoids. Suitable retinoids may include isotretinoin, acitretin, and tazarotene.
Another class of optional hair growth stimulants for use herein are triterpenes such as, for example, those disclosed in Bradbury et al., U.S. Patent Application Serial No. 09/353,408, "Method for Regulating Hair Growth", filed July 15, 1999 and Bradbury et al., U.S. Patent Application Serial No. 09/353,409, "Compositions Which Contain Triterpenes for Regulating Hair Growth", filed July 15, 1999, each incorporated by reference in their entirety.

Other classes of optional hair growth stimulants for use herein include flavinoids, ascomycin derivatives and analogs, histamine antagonists such as diphenhydramine hydrochloride, other triterpenes such as oleanolic acid and ursolic acid and those described in U.S. Patent 5,529,769, JP 10017431, WO 95/35103, U.S. Patent 5,468,888, JP 09067253, WO 92/09262, JP 62093215, U.S. Patent 5,631,282, U.S. Patent 5,679,705, JP 08193094, saponins such as those described in EP 0,558,509 to Bonte et al., published September 8, 1993 and WO 97/01346 to Bonte et al, published January 16, 1997 (both of which are herein incorporated by reference in their entirety), proteoglycanase or glycosaminoglycanase inhibitors such as those described in U.S. Patents 5,015,470, issued May 14, 1991, U.S. Patent 5,300,284, issued April 5, 1994 and U.S. Patent 5,185,325, issued February 9, 1993 (all of which are herein incorporated in their entirety by reference) estrogen agonists and antagonists, pseudoterpins, cytokine and growth factor promoters, analogs or inhibitors such as interleukin-1 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 panthenol, interferon agonists and antagonists, hydroxyacids such as those described in U.S. Patent 5,550,158, benzophenones, and hydantoin anticonvulsants such as phenytoin.


Non-limiting examples of penetration enhancers which may be used in the compositions herein include, for example, 2-methyl propan-2-ol, propan-2-ol, ethyl-2-hydroxypropanoate, hexan-2,5-diol, POE(2) ethyl ether, di(2-hydroxypropyl) ether, pentan-2,4-diol, acetone, POE(2) methyl ether, 2-hydroxypropionic acid, 2-hydroxyoctanoic acid, propan-1-ol, 1,4-dioxane, tetrahydrofuran, butan-1,4-diol, propylene glycol dipelargonate, polyoxypropylene 15 stearyl ether, octyl alcohol, POE ester of oleyl alcohol, oleyl alcohol, lauryl alcohol, dioctyl adipate, dicapryl adipate, di-isopropyl adipate, di-isopropyl sebacate, dibutyl sebacate, diethyl sebacate, dimethyl sebacate, dioctyl sebacate, dibutyl suberate, dioctyl azelate, dibenzyl sebacate, dibutyl phthalate, dibutyl azelate, ethyl myristate, dimethyl azelate, butyl myristate, dibutyl succinate, didecyl phthalate, decyl oleate, ethyl caproate, ethyl salicylate, iso-propyl palmitate, ethyl laurate, 2-ethyl-hexyl pelargonate, iso-propyl 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, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, phosphine oxides, sugar esters, tetrahydrofurfural alcohol, urea, diethyl-m-toluamide, and, 1-dodecylazacyloheptan-2-one.

In all of the foregoing, of course, the compounds used in the present method can be administered alone or as mixtures, and the compositions may further include additional drugs or excipients as appropriate for the indication.

The present invention further relates to kits comprising a compound and / or composition herein and information and / or instructions by words, pictures, and / or the like, that use of the kit will provide treatment for hair loss in mammals (particularly humans) including, for example, arresting and / or reversing hair loss and / or promoting hair growth. In addition or in the alternative, the kit may comprise a compound and / or composition herein and information and / or instructions regarding methods of application of the compound and / or composition, preferably with the benefit of treating hair loss in mammals.

Examples of Composition Administration

The following examples do not limit the invention, but provide guidance to the skilled artisan to perform the methods of the present invention. In each example, a “compound” other than the one mentioned may be substituted in the example by one having a structure as described herein with similar results.
Example A

A composition for topical administration is made, comprising:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound of Example 3</td>
<td>5 %</td>
</tr>
<tr>
<td>Ethanol</td>
<td>57 %</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td>19 %</td>
</tr>
<tr>
<td>Dimethyl Isosorbide</td>
<td>19 %</td>
</tr>
</tbody>
</table>

A human male subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 6 weeks, the above composition is daily administered topicaly to the subject.

Example B


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 C

A shampoo is made, comprising:

<table>
<thead>
<tr>
<th>Component</th>
<th>Ex. C-1</th>
<th>Ex. C-2</th>
<th>Ex. C-3</th>
<th>Ex. C-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonium Lauryl Sulfate</td>
<td>11.5 %</td>
<td>11.5 %</td>
<td>9.5 %</td>
<td>7.5 %</td>
</tr>
<tr>
<td>Ammonium Laureth Sulfate</td>
<td>4 %</td>
<td>3 %</td>
<td>2 %</td>
<td>2 %</td>
</tr>
<tr>
<td>Cocamide MEA</td>
<td>2 %</td>
<td>2 %</td>
<td>2 %</td>
<td>2 %</td>
</tr>
<tr>
<td>Ethylene Glycol Distearate</td>
<td>2 %</td>
<td>2 %</td>
<td>2 %</td>
<td>2 %</td>
</tr>
<tr>
<td>Cetyl Alcohol</td>
<td>2 %</td>
<td>2 %</td>
<td>2 %</td>
<td>2 %</td>
</tr>
<tr>
<td>Stearyl Alcohol</td>
<td>1.2 %</td>
<td>1.2 %</td>
<td>1.2 %</td>
<td>1.2 %</td>
</tr>
<tr>
<td>Glycerin</td>
<td>1 %</td>
<td>1 %</td>
<td>1 %</td>
<td>1 %</td>
</tr>
<tr>
<td>Polyquaternium 10</td>
<td>0.5 %</td>
<td>0.25 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Polyquaternium 24</td>
<td>-</td>
<td>-</td>
<td>0.5 %</td>
<td>0.25 %</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>0.1 %</td>
<td>0.1 %</td>
<td>0.1 %</td>
<td>0.1 %</td>
</tr>
<tr>
<td>Sucrose Polyesters of Cottonate Fatty Acid</td>
<td>3 %</td>
<td>3 %</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
A human male subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 12 weeks, the above shampoo is used daily by the subject.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>1 %</th>
<th>3 %</th>
<th>1.5 %</th>
<th>1.5 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocamino propyl Betaine</td>
<td>-</td>
<td></td>
<td>1 %</td>
<td>3 %</td>
</tr>
<tr>
<td>Lauryl Dimethyl Amine Oxide</td>
<td>1.5 %</td>
<td>1.5 %</td>
<td>1.5 %</td>
<td>1.5 %</td>
</tr>
<tr>
<td>Decyl Polyglucose</td>
<td>-</td>
<td>-</td>
<td>1 %</td>
<td>1 %</td>
</tr>
<tr>
<td>DMDM Hydantoin</td>
<td>0.15 %</td>
<td>0.15 %</td>
<td>0.15 %</td>
<td>0.15 %</td>
</tr>
<tr>
<td>Compound of Example 4b</td>
<td>-</td>
<td>5 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Compound of Example 3</td>
<td>-</td>
<td>-</td>
<td>3 %</td>
<td>-</td>
</tr>
<tr>
<td>Compound of Example 5b</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6 %</td>
</tr>
<tr>
<td>Phenoxyethanol</td>
<td>0.5 %</td>
<td>0.5 %</td>
<td>0.5 %</td>
<td>0.5 %</td>
</tr>
<tr>
<td>Fragrance</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</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>
What is claimed is:

1. Use, in the manufacture of a composition to treat hair loss, of a compound characterized by the structure:

M-L-Q

and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein M and Q are each, independently, radicals of structure I and wherein L is a linker moiety which covalently links M and Q together; wherein structure I is:

\[
\begin{array}{c}
  \text{G} \\
  \text{C}_A \equiv \text{O}
\end{array}
\]

wherein:

(a) each G is, independently, selected from the group consisting of nil, aliphatic, heteroaliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, and

\[
\begin{array}{c}
  \text{B}_1 \\
  \text{B}_2
\end{array}
\]

(b) each n is, independently, an integer selected from the group consisting of 1 and 2;

(c) each X is independently selected from the group consisting of -O-, -NH-, and -CH₂-;

(d) each R₁ is, independently, selected from the group consisting of aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aryl, and heteroaryl;

(e) each Cₐ is a carbon atom;

(f) each Cₐ is a carbon atom;

(g) each B₁ and B₂ is, independently, selected from the group consisting of hydrogen, aliphatic, heteroaliphatic, aryl, and heteroaryl; or wherein each B₁ and B₂ of the same G are, together, a carbonyl group; and

(h) each R₂ is, independently, selected from the group consisting of nil, aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aryl, and heteroaryl;

wherein when G of M is nil, L is covalently attached to Cₐ of M; wherein when G of Q is nil, L is covalently attached to Cₐ of Q; wherein when B₁ and B₂ of M are, together, a carbonyl group
and \( R_2 \) is nil, \( L \) is covalently attached to \( C_B \) of \( M \); and wherein when \( B_1 \) and \( B_2 \) of \( Q \) are, together, a carbonyl group and \( R_2 \) is nil, \( L \) is covalently attached to \( C_B \) of \( Q \).

2. A use according to claim 1 wherein each \( G \) is:

\[
\begin{align*}
\text{B}_1 & \quad \text{C}_B \\
\text{B}_2 & \quad \text{R}_2
\end{align*}
\]

and wherein each \( B_1 \) and \( B_2 \) of each \( G \) are, together, a carbonyl group.

3. A use according to claim 2 wherein \( M \) and \( Q \) are equivalent.

4. A use according to claim 3 wherein each \( R_1 \) is:

\[
\begin{align*}
\text{R}_4 & \\
\text{R}_5 & \\
\text{R}_6
\end{align*}
\]

wherein:

(a) each \( R_4 \) is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl, and heteroaryl optionally substituted with aryl;

(b) each \( R_5 \) is \( C_1 \) - \( C_8 \) alkyl; and

(c) each \( R_6 \) is selected from the group consisting of alkyl, heteroalkyl, heterocycle, aryl, and heteroaryl optionally substituted with aryl.

5. A use according to claim 4 wherein each \( R_2 \) is nil.

6. A use according to claim 1 wherein each \( G \) is:

\[
\begin{align*}
\text{B}_1 & \quad \text{C}_B \\
\text{B}_2 & \quad \text{R}_2
\end{align*}
\]

and wherein each \( B_1 \) and \( B_2 \) is, independently, selected from the group consisting of hydrogen, aliphatic, heteroaliphatic, aryl, and heteroaryl.
7. A use according to claim 6 wherein each $B_1$ and $B_2$ is hydrogen.

8. A use according to claim 7 wherein $M$ and $Q$ are equivalent.

9. A use according to claim 8 wherein each $R_1$ is:

\[
\begin{array}{c}
R_4 \\
\hline
R_5 \\
R_6
\end{array}
\]

wherein:

(a) each $R_4$ is selected from the group consisting of hydrogen, alkyl, heteroalkyl, aryl, and heteroaryl optionally substituted with aryl;

(b) each $R_5$ is C\textsubscript{1} - C\textsubscript{8} alkyl; and

(c) each $R_6$ is selected from the group consisting of alkyl, heteroalkyl, heterocycle, aryl, and heteroaryl optionally substituted with aryl.

10. A use according to claim 1 wherein the composition is administered by a method selected from the group consisting of topically and orally.

11. A compound characterized by the structure:

\[
\text{M-L-Q}
\]

and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein $M$ and $Q$ are each, independently, radicals of structure II and wherein $L$ is a linker moiety which covalently links $M$ and $Q$ together; and wherein structure II is:

\[
\begin{align*}
\text{X} & \text{R}_1 \\
\text{G} \backsim \text{O} \\
\text{C}_\text{A} \backsim \text{O}
\end{align*}
\]

wherein:

(a) each $G$ is independently selected from nil and

\[
\text{O} \backsim \text{C}_\text{B}
\]

(b) each $n$ is, independently, an integer selected from 1 and 2;
(c) each X is independently selected from -O-, -NH-, and -CH₂-;
(d) each R₁ is, independently, selected from aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aryl, and heteroaryl;
(e) each Cₐ is a carbon atom;
(f) each Cₐ is a carbon atom;
(g) L is aryl;

wherein when G of M is nil, L is covalently attached to Cₐ of M; wherein when G of Q is nil, L is covalently attached to Cₐ of Q; wherein when G of M is:

```
O=C_B
```

L is covalently attached to Cₐ of M; and wherein when G of Q is:

```
O=C_B
```

L is covalently attached to Cₐ of Q.

12. A compound characterized by the structure:

```
M-L-Q
```

and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein M and Q are each, independently, radicals of structure III and wherein L is a linker moiety which covalently links M and Q together; wherein structure III is:

```
\begin{center}
\begin{tikzpicture}
\node (x) at (0,0) {$X$};
\node (r1) at (-1,-0.5) {$R_1$};
\node (g) at (-2,-1) {$G$};
\node (n) at (-3,-2) {$n$};
\node (b1) at (-4,-3) {$B_1$};
\node (b2) at (-3,-3.5) {$B_2$};
\node (r2) at (-2,-4) {$R_2$};
\draw (x) -- (r1);
\draw (x) -- (g);
\draw (r1) -- (b1);
\draw (b1) -- (b2);
\draw (b2) -- (r2);
\end{tikzpicture}
\end{center}
```

wherein:

(a) each G is independently selected from aliphatic, heteroaliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, and

```
\begin{center}
\begin{tikzpicture}
\node (r1) at (-1,-0.5) {$R_1$};
\node (b1) at (-2,-1) {$B_1$};
\node (b2) at (-3,-1.5) {$B_2$};
\node (r2) at (-4,-2) {$R_2$};
\draw (r1) -- (b1);
\draw (b1) -- (b2);
\draw (b2) -- (r2);
\end{tikzpicture}
\end{center}
```

(b) each n is, independently, an integer selected from the group consisting of 1 and 2;
(c) each X is independently selected from the group consisting of -O-, -NH-, and -CH₂-;
(d) each $B_1$ and $B_2$ is, independently, selected from the group consisting of hydrogen, aliphatic, heteroaliphatic, aryl, and heteroaryl; or wherein each $B_1$ and $B_2$ of the same G are, together, a carbonyl group;

(e) each $R_1$ is, independently, selected from the group consisting of aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aryl, and heteroaryl;

(f) each $R_2$ is, independently, selected from the group consisting of aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aryl, and heteroaryl; and

(g) $L$ is selected from the group consisting of bond, -O-, -S-, and -NH-. 
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7   C07D211/60   C07D207/16   A61K7/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7   C07D   A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of data base and, where practical, search terms used)

CHEMABS Data, BEILSTEIN Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<tr>
<td>X</td>
<td>EP 0 915 088 A (F. HOFFMANN-LA ROCHE AG) 12 May 1999 (1999-05-12) examples 66a, 67a, 95b</td>
<td>11, 12</td>
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<td>X</td>
<td>US 4 663 641 A (K. IYYAMA ET AL) 5 May 1987 (1987-05-05) column 9, lines 12-14</td>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:
  *A* document defining the general state of the art which is not considered to be of particular relevance
  *E* earlier document but published on or after the international filing date
  *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  *O* document referring to an oral disclosure, use, exhibition or other means
  *P* document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search: 1 December 2000

Date of mailing of the international search report: 19/12/2000

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Fax: (+31-70) 340-3016

Authorized officer

Van Amsterdam, L
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## INTERNATIONAL SEARCH REPORT

### Patent document cited in search report

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