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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 July 2006 (13.07.2006)

PCT

(10) International Publication Number
WO 2006/074379 A2

(51) International Patent Classification:
A61K 8/36 (2006.01)

(21) International Application Number:
PCT/US2006/000476

(22) International Filing Date: 6 January 2006 (06.01.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/642,075 7 January 2005 (07.01.2005) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/642,075 (CON)
Filed on 7 January 2005 (07.01.2005)

(71) Applicant *(for all designated States except US)*: **AZAYA THERAPEUTICS, INC.** [US/US]; 9901 IH10 West, Suite 800, San Antonio, TX 78230 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **STREEPER, Robert, T.** [US/US]; 18745 IH-35 N., Schertz, TX 78154 (US). **SINGH, Chandra, U.** [US/US]; 4 Thornhurst Road, San Antonio, TX 78218 (US).

(74) Agent: **PARKER, David, L.**; FULBRIGHT & JAWORSKI L.L.P., 600 Congress Avenue, Suite 2400, Austin, Texas 78701 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** METHODS AND COMPOSITIONS INVOLVING ESTERS OF AZELAIC ACID AND OTHER DICARBOXYLIC ACIDS

(57) **Abstract:** The present invention relates to formulations of azelaic acid esters and other dicarboxylic acid esters, and their derivatives. In preferred embodiments, the esters have the general Formula (I) wherein R_1 and R_2 are selected from hydrogen, alkyl groups of up to about 18 carbon atoms and aryl groups of up to about 18 carbon atoms and alkylene group of up to about 18 carbon atoms and an arylene group of up to about 18 carbon atoms. The alkyl, aryl, alkylene and aryl groups may be substituted or unsubstituted, branched or straight chains. In addition, R_1 and R_2 may contain heteroatoms and may be straight chained or branched, n is an integer from 1-16, and R_1 and R_2 are not simultaneously hydrogen. $R_2OOC\text{-}(CH_2)n\text{-}COOR_1$ (I). The azelaic acid derivatives of Formula I of this invention are certain derivatives of azelaic acid and other alkyl geminal diacids which possess a desirable high lipophilicity and biphasic solubility in comparison to the parent compound, azelaic acid, and which are cleaved enzymatically to azelaic acid. Compounds produced from the compounds of Formula (I) by the enzymatic hydrolysis of the R_1 and R_2 groups are useful as anti-bacterial agents in mammals in vivo and have been contemplated to be used in the treatment of skin disease.

WO 2006/074379 A2

DESCRIPTION

METHODS AND COMPOSITIONS INVOLVING ESTERS OF AZELAIC ACID AND OTHER DICARBOXYLIC ACIDS

BACKGROUND OF THE INVENTION

This patent application is related to U.S. Provisional Patent 60/642,075, filed on January 7, 2005, which is herein incorporated by reference in its entirety.

Azelaic acid is a naturally occurring, straight chain, 9 carbon atom, saturated dicarboxylic acid obtained by oxidation of oleic acid or by chemical, physical or biological oxidation of free and esterified fatty acids. It is found also in small amounts in the urine of normal individuals (Mortensen 1984). *In vitro*, azelaic acid has been shown to be a competitive inhibitor of a number of oxidoreduction enzymes such as tyrosinase (Nazzaro-Porro *et al.*, 1979), thioredoxin reductase (Schallreuter 1987), DNA polymerase (Galhaup 1989), and also of mitochondrial oxidoreductases in the respiratory chain (Passi *et al.* 1984). In addition, azelaic acid is a potent inhibitor of 5-α-reductase (Stamatidas *et al.* 1988). Azelaic acid is a scavenger of toxic oxygen species and also inhibits oxyradical activity in cell cultures (Passi *et al.* 1991& 1989).

Azelaic acid has been used clinically for many years in the treatment of acne vulgaris as well as in hyperpigmentary skin disorders (Fitton 1991). Azelaic acid has also has recently been studied for the treatment of papulopustular rosacea (Maddin 1999).

While azelaic acid has been used primarily in the treatment of dermatological conditions, because of some of its mechanisms of action, it could have further clinical utility in conditions unrelated to the skin. Azelaic acid has been shown to have antiproliferative and cytotoxic action on the following tumor cell lines: human cutaneous malignant melanoma (Zaffaroni *et al.* 1990), human choroidal melanoma (Breatimach *et al.* 1989), human squamous cell carcinoma (Paetzold *et al.* 1989), and fibroblastic lines (Geier *et al.* 1986). Azelaic acid would also be expected to have utility in the prevention and treatment of skin cancer as well as solar keratosis. Because of its mechanism of action as a potent inhibitor of 5-□-reductase, azelaic

acid may be applicable to the treatment and prevention of benign enlargement as well as cancer of the prostate and other conditions in which 5-□-reductase is elevated.

While azelaic acid is somewhat soluble in water, cosmetic oils and alcohols, each of these solvents has serious limitations. Thus, water only marginally dissolves azelaic acid so that a water and azelaic acid solution would contain a maximum of about 0.24% by weight (w/w) azelaic acid, not likely enough to be effective. Azelaic acid has little or no solubility in cosmetic oils. Alcohols are good solvents but are unsatisfactory because large amounts of alcohol, *e.g.*, isopropyl alcohol, in a topical composition have the undesirable side effect of drying the skin. Indeed, some alcohols, *e.g.*, ethyl alcohol, render azelaic acid unstable at normal temperatures resulting in a totally ineffective composition. For the dermatological use of azelaic acid, the problem of solubility in suitable solvents remains.

U.S. Patents No. 4,292,326, 4,386,104, and U.S. Pat. No. 4,818,768, describe azelaic acid as well as other dicarboxylic acids in the treatment of acne and melanocyclic hyperpigmentary dermatoses. The azelaic acid is dispersed in a cream base.

U.S. Patents 4,713,394 and 4,885,282 describe azelaic acid as well as other dicarboxylic acids used in the treatment of non-acne inflammatory dermatoses and infectious cutaneous diseases such as rosacea, perioral dermatitis, eczema, seborrheic dermatitis, psoriasis, tinea cruris, flat warts, and alopecia areata. One of Thomfeldts' formulations comprises azelaic acid disposed in a large proportion of ethanol. While ethyl alcohol dissolves azelaic acid, it also renders the azelaic acid unstable at normal temperatures, which means that it will not provide a marketable product. Thornfeldt's second formulation comprises a complete dispersion of azelaic acid.

U.S. Patent 6,451,773 describes a composition for treating acneiform eruption containing a chitosan having a molecular weight ranging from about 500,000 to about 5,000,000 g/mole and a degree of deacylation greater than 80% and an acid-form active ingredient such as azelaic acid for treating acne. U.S. Patent 6,734,210 discloses that stable salts of azelaic acid with polycations such as chitosan are water-soluble, therapeutically more efficacious and are valuable for use as active constituents in pharmaceutical as well as cosmeceutical compositions.

Venkateswaran, U.S. Patent No. 5,549,888, teaches a solution of active ingredients which includes azelaic acid and a water soluble glycol. The solution uses glycol in combination with ethyl alcohol to solubilize the azelaic acid. As stated previously, the presence of ethyl alcohol with azelaic acid can destabilize the azelaic acid. Moreover, because the composition contains ethyl alcohol, the preparation of a non-drying, aesthetically pleasing formulation would be difficult. Venkateswaran also teaches that the formulation has a pH between 2.5 and 4.0. This low pH range can have an irritating effect on the skin. Again, this patent also does not teach the use of azelaic acid esters. Indeed, a search of the patent as well as the scientific literature does not reveal any prior use of the esters of azelaic acid that are the object of this present invention.

The art has yet to find a formulation for completely solubilizing azelaic acid at normal temperatures without sacrificing the stability of the solubilized azelaic acid. Solubilized azelaic acid must remain stable at normal temperatures in order to provide a marketable product. Without a stable, completely solubilized formula of azelaic acid, the benefits of azelaic acid are unavailable to many users who experience the burning, stinging and redness of the skin associated with exposure to high levels of undissolved dispersed azelaic acid having an inherent low pH.

The present invention can provide completely lipid soluble and stable esters of azelaic acid and other dicarboxylic acids. The lipid soluble azelaic acid esters and other dicarboxylic acid esters may be more bioavailable when administered by routes other than topically. These esters of the present invention would have significant utility over salts of azelaic acid currently described in the patent and scientific literature. These and still further objects as shall hereinafter appear are fulfilled by the present invention in a remarkably unexpected fashion. The authors of this present invention have surprisingly and unexpectedly solved the problem of solubility of azelaic acid and other dicarboxylic acids with the synthesis of esters of these carboxylic acids.

SUMMARY OF THE INVENTION

The present invention concerns methods and pharmaceutical compositions directed to dicarboxylic acid esters, geminal diols, and omega-hydroxy carboxylic acids.

In one aspect, the present invention provides methods for treating skin conditions. The methods involve administering to a patient in need of such treatment a therapeutically effective amount of a dicarboxylic acid ester, or a pharmaceutically acceptable salt thereof.

As used herein, the term "dicarboxylic acid ester" refers to a dicarboxylic acid ester or a pharmaceutically acceptable salt thereof.

As used herein, the term "therapeutically effective amount" means an amount that will result in an improvement or a desired change in condition for which an active ingredient is administered, when the ingredient is administered once or over a period of time. As is known, the amount will vary depending on such particulars as the type of condition being treated, the specific active ingredient, the severity of the condition, and the characteristics of the patient.

In some embodiments, the dicarboxylic acid ester is dissolved in a lipophilic medium. The lipophilic medium can be a triglyceride, an alcohol, a polyol, an amide, an ester, or a propylene glycol ether, or a mixture thereof. Examples of triglycerides include but are not limited to almond oil; babassu oil; borage oil; blackcurrant seed oil; canola oil; castor oil; coconut oil; corn oil; cottonseed oil; evening primrose oil; grapeseed oil; groundnut oil; mustard seed oil; olive oil; palm oil; palm kernel oil; peanut oil; rapeseed oil; safflower oil; sesame oil; shark liver oil; soybean oil; sunflower oil; hydrogenated castor oil; hydrogenated coconut oil; hydrogenated palm oil; hydrogenated soybean oil; hydrogenated vegetable oil; hydrogenated cottonseed and castor oil; partially hydrogenated soybean oil; soy oil; glyceryl tricaproate; glyceryl tricaprylate; glyceryl tricaprate; glyceryl triundecanoate; glyceryl trilaurate; glyceryl trioleate; glyceryl trilinoleate; glyceryl trilinolenate; glyceryl tricaprylate/caprate; glyceryl tricaprylate/caprate/laurate; glyceryl tricaprylate/caprate/linoleate; glyceryl tricaprylate/caprate/stearate; saturated polyglycolized glycerides; linoleic glycerides; caprylic/capric glycerides; modified

triglycerides; fractionated triglycerides; and mixtures thereof. Examples of alcohols or polyols include but are not limited to ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, maltol, maltodextrins, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulosic polymers, cyclodextrins, and mixtures thereof. Examples of amides include but are not limited to 2-pyrrolidone, 2-piperidone, ε-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide, polyvinylpyrrolidone, and mixtures thereof. Examples of esters include but are not limited to ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ϵ-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof, and mixtures thereof.

In other embodiments, the dicarboxylic acid ester is dissolved in a medium essentially free of ethanol and/or isopropanol. In still further embodiments, the dicarboxylic acid ester is dissolved in a lipophilic medium that is essentially free of ethanol and/or isopropanol.

The skin condition for treatment can include acne, psoriasis, rosacea, aging of the skin, alopecia, solar keratoses, bacterial infection, malignant melanoma, melasma, lentigo maligna, hyperpigmentation, wrinkles, blemishes, lesions of the skin, perioral dermatitis, mycoplasma infection or impetigo. Preferably, the skin condition is acne or psoriasis.

The dicarboxylic acid ester can be administered orally, parenterally, rectally, nasally, buccally, transdermally, via an implanted reservoir, or topically. Preferably, the ester is administered by application to an affected area of skin. In preferred embodiments, the dicarboxylic acid ester is administered topically in an ointment, crème, lotion, paste, gel, drops, spray, liquid, shampoo, transdermal patch, or the like.

The dicarboxylic acid ester can be administered as a pharmaceutical composition containing a therapeutically effective amount of the dicarboxylic acid ester, or a pharmaceutically acceptable salt thereof. Thus, a pharmaceutical

composition containing the dicarboxylic acid ester, or pharmaceutically acceptable salt thereof, is provided in accordance with the present invention.

In particular embodiments, the dicarboxylic acid ester is a compound of formula (I)

$$R_2OOC\text{-}(CH_2)n\text{-}COOR_1 \qquad (I)$$

where R_1 and R_2 are each independently hydrogen, an alkyl group of up to 18 carbon atoms, an aryl group of up to 18 carbon atoms, an alkylene group of up to 18 carbon atoms, an arylene group of up to 18 carbon atoms, a cyclic alkyl group, a phenalkyl group, an alkenyl group or a heteroaryl group. Each of these groups can be substituted or non-substituted, and straight chained or branched. In formula (I), n is an integer from 1 to 16, R_1 and R_2 are not simultaneously hydrogen, and R_1 and R_2 can each independently contain one or more heteroatoms. As used herein, "heteroatom" means an atom other than carbon or hydrogen.

Preferably, R_1 and R_2 are each independently hydrogen or a substituted or non-substituted alkyl, aryl, alkylene or arylene group of up to 18 carbon atoms.

Also, n is preferably 5, 7, 9, 10, 11, 12, 13, 14 or 16. More preferably, n is 5, 7, 9, 11 or 13. Even more preferably, n is 7.

Examples of R_1 and R_2 groups include such groups as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, hexadecyl, octadecyl, palmityl, stearyl, methoxyethyl, ethoxyethyl, benzyl, glyceryl and nicotninyl groups. In preferred embodiments, R_1 and R_2 are each independently a methyl, ethyl, propyl, isopropyl, isobutyl, hexyl, hexadecyl, or octadecyl group. In particularly preferred embodiments, R_1 is the same as R_2.

In other preferred embodiments, R_1 is a methyl, ethyl, propyl, isopropyl, isobutyl, hexyl, hexadecyl, or octadecyl group, and R_2 is hydrogen.

In a further aspect, the present invention provides another method for treating a skin condition. The method involves administering to a patient in need of such treatment a therapeutically effective amount of a geminal diol or a pharmaceutically acceptable salt thereof. The geminal diol is a compound of formula (II)

$$HO\text{-}(CH_2)n\text{-}OH \qquad (II)$$

where n is an integer from 1-16.

In yet another aspect, the present invention provides a method for treating a skin condition, where the method involves administering to a patient in need of such treatment a therapeutically effective amount of an omega-hydroxy carboxylic acid or a pharmaceutically acceptable salt thereof. The omega-hydroxy carboxylic acid is a compound of formula (III)

$$HO\text{-}(CH_2)n\text{-}COOR \quad (III)$$

where n is an integer from 1-16, and R is an alkyl group of up to 18 carbon atoms, an aryl group of up to 18 carbon atoms, an alkylene group of up to 18 carbon atoms, or an arylene group of up to 18 carbon atoms. Each of these groups can be substituted or non-substituted, and branched or straight chained. In addition, R can contain one or more heteroatoms.

Examples of R include such groups as methyl, ethyl, propyl, isopropyl, isobutyl, hexyl, hexadecyl and octadecyl groups.

In preferred embodiments, n is 5, 7, 9, 10, 11, 12 13, 14 or 16. More preferably, n is 5, 7, 9, 11 or 13. Even more preferably, n is 7.

As used herein, the term "geminal diol" refers to a geminal diol or a pharmaceutically acceptable salt thereof, and the term "omega-hydroxy carboxylic acid" refers to an omega-hydroxy carboxylic acid or a pharmaceutically acceptable salt thereof.

In particular embodiments, the geminal diol or the omega-hydroxy carboxylic acid is dissolved in a lipophilic medium, in a medium essentially free of ethanol and/or isopropanol, or in a lipophilic medium essentially free of ethanol and/or isopropanol.

The skin condition for treatment by the geminal diol or the omega-hydroxy carboxylic acid can include acne, psoriasis, rosacea, aging of the skin, alopecia, solar keratoses, bacterial infection, malignant melanoma, melasma, lentigo maligna, hyperpigmentation, wrinkles, blemishes, lesions of the skin, perioral dermatitis, or impetigo. Preferably, the skin condition is acne or psoriasis.

The geminal diol or the omega-hydroxy carboxylic acid can be administered orally, parenterally, rectally, nasally, buccally, transdermally, via an implanted reservoir, or topically. The compound is preferably administered by applying it to an affected area of skin. In preferred embodiments, the compound is administered topically in an ointment, crème, lotion, paste, gel, drops, spray, liquid, shampoo, or transdermal patch.

The geminal diol or the omega-hydroxy carboxylic acid can be administered in a pharmaceutical composition containing a therapeutically effective amount of the geminal diol or the omega-hydroxy carboxylic acid, or a pharmaceutically acceptable salt thereof. Thus, a pharmaceutical composition containing the geminal diol or the omega-hydroxy carboxylic acid, or a pharmaceutically acceptable salt thereof, is provided in accordance with the present invention.

The present invention discloses lipid soluble esters of azelaic acid and other dicarboxylic acids, methods for the use thereof and synthetic methods for their preparation. The esters of azelaic acid of this present invention have utility in increasing blood and other tissue or fluid levels of azelaic acid, as well as in treating or preventing a wide variety of conditions related to the aforementioned mechanisms of action of azelaic acid.

Thus in one embodiment, an azelaic acid ester is administered to a warm-blooded animal in need thereof. In yet a further embodiment, an azelaic acid ester is administered to a warm blooded animal to prevent and or treat the following conditions: Aging of the skin, cancer, HIV, alopecia, solar keratosis, benign prostatic hypertrophy, prostate cancer, acne, bacterial infection, malignant melanoma, hair loss, bladder cancer, rosacea, conditions in which tyrosinase activity needs to be modulated, melasma, conditions in which 5-□-reductase activity needs to be modulated, conditions related to excessive expression of reactive oxygen species such as stroke, heart attack other pathological ischemias, lentigo maligna, hyperpigmentation associated with burns and other physical trauma, viral infections, and herpes labialis and genitalis. Other aspects of the present invention will become evident upon reference to the following detailed description.

In a preferred embodiment, the pharmaceutical composition comprises at least one highly lipophilic azelaic derivative. It will, of course, be understood that the

composition may further comprise a second highly lipophilic azelaic acid derivative, and/or one or more other pharmacologically-active compounds, and particularly one or more anti-tumor, anti-fungal, anti-viral or anti-bacterial compounds. The methods of the invention may thus entail the administration of one, two, three, or more, of highly lipophilic azelaic derivatives in conjunction with other pharmacologically active molecules. The maximum number of types of molecules that may be administered is limited only by practical considerations, such as the particular effects of each compound.

The invention further includes the use of the azelaic acid esters according to Formula (I) in the manufacture of a medicament for oral, topical, parenteral delivery with the intention of relieving disease conditions in a mammal.

It is contemplated that any method or composition described herein can be implemented with respect to any other method or composition described herein.

The use of the word "a" or "an" when used in conjunction with the term "comprising" in the numbered and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

The use of the term "or" in the numbered claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternative are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or."

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

The term "treat" or "treatment" means that the symptoms associated with one or more conditions mentioned above are alleviated or reduced in severity or frequency

and the term "prevent" means that subsequent occurrences of such symptoms are avoided or that the frequency between such occurrences is prolonged.

The azelaic acid ester derivatives of the present invention are certain esters that show a higher lipophilicity and biphase solubility than the active parent compound and hence are better able to be incorporated into a pharmaceutical formulation and which are capable of reverting to the active azelaic acid after the administration through enzymatic or chemical hydrolysis. The compounds of Formula (I) used in the present invention are exemplified by esters of azelaic acid and are highly lipophilic in properties suitable for incorporation into the present inventive formulations.

Examples of straight-chain alkyl groups in Formula (I) include methyl, ethyl, propyl, butyl, hexyl, heptyl, octyl, dodecyl, palmityl, stearyl and the like groups.

Examples of branched chain alkyl groups include isopropyl, *sec*-butyl, *t*-butyl, 2-methylbutyl, 2-pentyl, 3-pentyl and the like groups.

Examples of cyclic alkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups.

Examples of "alkenyl" groups include vinyl (ethenyl), 1-propenyl, *i*-butenyl, pentenyl, hexenyl, *n*-decenyl and *c*-pentenyl and the like.

The groups may be substituted, generally with 1 or 2 substituents, wherein the substituents are independently selected from halo, hydroxy, alkoxy, amino, mono- and dialkylamino, nitro, carboxyl, alkoxycarbonyl, and cyano groups.

By the expression "phenalkyl groups wherein the alkyl moiety contains 1 to 3 or more carbon atoms" is meant benzyl, phenethyl and phenylpropyl groups wherein the phenyl moiety may be substituted. When substituted, the phenyl moiety of the phenalkyl group may contain independently from 1 to 3 or more alkyl, hydroxy, alkoxy, halo, amino, mono- and dialkylamino, nitro, carboxyl, alkoxycarbonyl and cyano groups.

Examples of "heteroaryl" are pyridinyl, thienyl or imidazolyl.

As noted herein, the expression "halo" is meant in the conventional sense to include F, Cl, Br, and I.

Among the compounds represented by the general Formula (I), preferred compounds are such in which R_1 and R_2 are the same and is one of the following groups:

methyl
ethyl
propyl
butyl
pentyl
hexyl
palmityl
stearyl
isopropyl
isobutyl
methoxyethyl
ethoxyethyl
benzyl
nicotinyl

Other preferred compounds are such in which R_1 is hydrogen and R_2 is one of the groups listed above, or R_2 is hydrogen and R_1 is one of these groups.

The compounds of Formula (I) are exemplified by esters (mono and di-esters) of azelaic acid formed either at C_1 or C_9, or at both carboxyl groups. Several esters of dicarboxylic acids have long been known and the information on the preparation or pharmacological activity of various esters of dicarboxylic acids can thus be found in the following references. However, these references or other information in the literature do not disclose or indicate the esters of azelaic acid and any utility of esters or other derivatives of azelaic acid as pro-drug forms suitable for oral and topical delivery of azelaic acid, nor any properties of the compounds that might indicate such utility.

The lipophilicity of a compound is measured in terms of the partition coefficient of the compound between aqueous and octanol phase and can be measured experimentally. Also, the lipophilicity can be computed using certain molecular

simulation software. The calculated value of the partition coefficient of morphine and its derivatives are shown in Table 1. As can be seen, the di-esters of azelaic acid are more lipophilic than azelaic acid.

TABLE 1. AlogP Value of Azelaic Acid Derivatives.

Compound	AlogP (Log value of the Partition Coefficient)
Azelaic Acid	1.92
Dimethyl-azelate	2.37
Diethyl-azelate	3.07
Dipropyl-azelate	4.12
Dihexyl-azelate	6.85
Di-(t-butyl)-azelate	4.24

As will be described below it has now surprisingly been found that compounds of Formula (I), in contrast to azelaic acid itself, are highly useful and can be used in ointments and creams at a therapeutically effective rate and extent of delivery similar to azelaic acid without any limitations associated with free azelaic acid.

The compounds of Formula (I) can be prepared by various methods as described in the literature for a number of azelaic acid esters (see the references cited above). A large number of methods are known to the art that will allow a skilled practioner to produce the claimed composition of matter or its analogs and homologs. Among these are for instance: The direct formation of the ester from the requisite acid and an alcohol. This condensation may be achieved by the dehydration of the reaction mixture with a suitable agent. Commonly used dehydrating agents and methods include, heat, concentrated acids such as sulfuric acid, acid anhydrides such

as phosphorous pentoxide, gaseous acids such as hydrogen chloride gas introduced into a solution of the acid in the requisite alcohol, solution chemistries formed by reaction mixtures such as iodine or bromine with sodium hypophosphite or red phosphorous that generate hydriodic acid *in-situ* which then goes on to promote the formation of the ester by dehydration or transient organohalide formation, and so on. This listing should not be taken as being all-inclusive or exhaustive for there are many additional dehydration mediated esterification methods are known to the art.

A second major set of synthetic strategies comprise the methods wherein an activated intermediate of either the acid or the alcohol is formed which is then further reacted with the appropriate esterifying acid or alcohol to produce the desired ester. Among these are reactions of an alcohol with an activated form of the acid. Activated forms of the acid include acid halides, acid anhydrides including both homo and hetero anhydrides, the reaction of the internal anhydride of the parent acid with the requisite alcohol, esters and anhydrides of both the acid and the alcohol which are formed by reaction of the requisite acid or alcohol with *p*-toluene sulfonyl chloride to produce the tosyl anhydride or ester which is subsequently reacted with the alcohol or acid respectively to produce the desired final ester. Similarly one could substitute a simple organic acid anhydride, such as acetic acid anhydride, for the *p*-toluene sulfonyl chloride. In addition one could start with one ester selected from among the desired compositions of matter and by the means of solution of the ester in a desired alcohol in the presence of an appropriate acidic or basic catalyst effect a conversion of the starting ester of the acid to an ester wherein the alcohol becomes that in which the reaction is carried out which method is also known as trans-esterification.

For example, one could start with the dimethyl ester of the acid and by solution of the ester in ethanol in the presence of an acid or base one could cause the facile formation of the diethyl ester of the acid. In addition, if a mixed ester of the acid were desired, one could utilize an appropriately composed solution of the two desired alcohols in any of the methods herein described.

Finally, one could resort to the use of halogenated intermediates or ingredients to form the required esters. For example, thionyl chloride will chlorinate both acids and alcohols, thereby resulting in the acyl and alkyl chlorides. These acyl and alkyl chlorides may then be further reacted with the desired alcohol or acid respectively to

produce the desired ester products. Other common halogenating agents include for example oxalyl chloride and the chlorides and bromides of phosphorous such as phosphorous penta or trichloride and penta or tribromide or phosphorous oxychloride.

Finally, it is commonly practiced to form esters through the action of a strong base on a mixture of the acid and the alcohol. Examples of strong bases include lithium aluminum hydride and other metal hydrides, alkali metal alkoxides such as sodium ethoxide and diisobutyl aluminum hydride and so on. Again this listing of materials and methods should not be interpreted to be limiting, exhaustive or all-inclusive but is merely presented for illustration of the claimed possible methods. In addition, any of the above methods may be used with appropriate modifications of the reactants and conditions to produce mono- esters of the diacid, homo-diesters of the diacid or hetero-diesters of the diacid.

One method that we have utilized for efficient preparation of the homo diester of azelaic acid is through dissolution of azelaic acid in anhydrous, absolute, 200 proof ethanol. Through this solution is passed with stirring at room temperature anhydrous hydrogen chloride gas at a slow rate. After several hours of reaction the solution becomes saturated with hydrogen chloride and the gas can be turned off. Stirring at room temperature is continued for a time ranging from a few minutes to several hours as is necessary to ensure quantitative formation of the desired ester. To drive the reaction to completion and drive off the dissolved hydrogen chloride the solution is moderately warmed to effect gentle reflux of the solvent on the walls of the reaction vessel. The hydrogen chloride is vented in a safe manner. The solution of the ester in alcohol is then reduced in volume by heat or vacuum distillation. The crude ester is then taken up in an appropriate solvent such as ethyl acetate. The solution of the ester in the solvent is then washed several times with water containing a base such as sodium bicarbonate to remove both the remaining hydrogen chloride and any un-reacted acidic reaction products or the starting acid. The solvent solution of the ester is then separated from the wash solutions and washed several additional times with pure water. The solutions are allowed to separate and the water is discarded. The ethyl acetate is then mixed with a suitable dessicant such as anhydrous magnesium sulfate to remove any remaining residual water. The solvent is then removed from the ester which in the case of the ethyl ester of azelaic acid is a clear slightly yellow oil having a not disagreeable aroma. The ester is then further purified, as by fractional

distillation at reduced pressure, and analyzed, as by gas chromatography mass spectrometry, to the degree necessary to produce an active pharmaceutical ingredient, (API), that is suitable for the treatment of mammalian health disorders, specifically disorders of the skin.

As mentioned above, this invention is generally directed to lipophilic esters of azelaic acid and other dicarboxylic acids. Such esters, when administered to a warm blooded animal in need thereof, can have utility in the prevention or treatment of conditions enumerated above in warm blooded animals, including humans.

It has now surprisingly been found that esters of azelaic acid and other dicarboxylic acids have good characteristics that are such as to render them particularly suitable both for use in pharmaceutical formulations and for preparative applications.

Owing to the simple conception and low cost of the present invention, the procedures described in this invention easily lend themselves to the adaptation of the preparation methods to an industrial scale.

Depending on the intended mode of administration, the pharmaceutical compositions may be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, creams, ointments, lotions or the like, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions can include an effective amount of the selected drugs in combination with a pharmaceutically acceptable carrier and, in addition, may include other pharmaceutical agents, adjuvants, diluents, buffers, etc. The compounds may thus be administered orally, parenterally, transdermally, rectally, nasally, buccally, topically or via an implanted reservoir in dosage formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term "parenteral" as used herein is intended to include subcutaneous, intravenous, and intramuscular injection. The amount of active compound administered will, of course, be dependent on the subject being treated, the subject's weight, the manner of administration and the judgment of the prescribing physician.

For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., an active compound as described herein and optional pharmaceutical adjuvants in an excipient, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan mono-laurate, triethanolamine sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, (Arthur Osol, editor), (1980), incorporated by reference herein. For oral administration, the composition will generally take the form of a tablet or capsule, or may be an aqueous or nonaqueous solution, suspension or syrup. Tablets and capsules are preferred oral administration forms. Tablets and capsules for oral use will generally include one or more commonly used carriers such as lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. When liquid suspensions are used, the active agent may be combined with emulsifying and suspending agents. If desired, flavoring, coloring and/or sweetening agents may be added as well. Other optional components for incorporation into an oral formulation herein include, but are not limited to, preservatives, suspending agents, thickening agents, and the like.

Parenteral administration, if used, is generally characterized by injection. Injectable formulations can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solubilization or suspension in liquid prior to injection, or as emulsions. Preferably, sterile injectable suspensions are formulated according to techniques known in the art using suitable carriers, dispersing or wetting agents and suspending agents. The sterile injectable formulation may also be a sterile injectable solution or a suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile,

fixed oils, fatty esters or polyols are conventionally employed as solvents or suspending media. A more recently revised approach for parenteral administration involves use of a slow release or sustained release system, such that a constant level of dosage is maintained. See, e.g., U.S. Pat. No. 3,710,795 to Higuchi *et al.*., which is incorporated by reference herein.

It is to be understood that the dicarboxylic acid esters, geminal diols, and omega-hydroxy carboxylic acids of the present invention may in particular circumstances be administered in combination with ingredients such as wetting agents, solvents, excipient or vehicle ingredients. Examples of such ingredients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, acrylates copolymers, isopropyl myristate, isopropyl palmitate, mineral oil, butter(s), aloe, talc, botanical oils, botanical juices, botanical extracts, botanical powders, other botanical derivatives, lanolin, urea, petroleum preparations, tar preparations, plant or animal fats, plant or animal oils, soaps, triglycerides, and keratin(s), and mixtures thereof.

Additionally, moisturizers, sunscreens, fragrances, dyes, thickening agents such as paraffin, jojoba, paba, and waxes, surfactants, humectants, occlusives, hygroscopic agents, emulsifiers, emollients, lipid-free cleansers, antioxidants and lipophilic agents, may be added to the present methods and compositions if desired.

Moreover, the dicarboxylic acid esters, geminal diols, and omega-hydroxy carboxylic acids of the present invention may in particular circumstances also be administered with other ingredients such as other agents that improve or eradicate itching, irritation, pain, inflammation, age spots, keratoses, wrinkles, and other blemishes, lesions of the skin, perioral dermatitis, or impetigo.

Examples of such additional agents include, but are not limited to, analgesics, anesthetics, antiacne agents, antibacterial agents, anti-yeast agents, anti-fungal agents, antiviral agents, antibiotic agents, porbiotic agents, anti-protozal agents, anti-pruritic agents, antidandruff agents, anti-dermatitis agents, anti-emetics, anti-inflammatory agents, anti-hyperkeratolyic agents, anti-dry skin agents, antiperspirants, anti-psoriatic agents, anti-seborrheic agents, hair conditioners, hair treatments, hair growth agents, anti-aging agents, anti-wrinkle agents, antihistamine agents, disinfectants, skin lightning agents, depigmenting agents, vitamins and vitamin derivatives, gamma-

linolenic acid (GLA), beta carotene, quercetin, asapalene, melaluca alternifolia, dimethicone, neomycin, corticosteroids, tanning agents, zinc/zinc oxides, sulfur agents, hormones, retinoids, clotrimazole, ketoconazole, miconazole, griseofulvin, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, monobenzone, erythidocaine, erythromycin, tetracycline, clindamycin, meclocline, hydroquinone, minocycline, naproxen, ibuprofen, theophylline, cromolyn, alburterol, retinoic acid and its derivatives, hydrocortisone and its derivatives, mornetasone, desonide, trimcinolone, predisolone, NUTRACORT® brand topical steroid application, salicylic acid, phospholipids, calamine, allantoin, isohexadelane, ceresin, galcipotriene, DOVONEX® brand dermatological preparation, anthralin, betamethasone valerate, betamethasone diproprionate, trimcinolone acetonide, fluocinonide, clobetasol propionate, benzoyl peroxide, crotamition, propranolon, promethanzine, vitamin A palmitate, vitamin E acetate, vitamin D and mixtures or derivatives thereof may be added to embodiments of the present invention to improve or alter their effectiveness.

U.S. Patent Nos. 6,667,045 to Dahle, 6,710,223 to Van Rijswijck , *et al..*, and 6,383,523 to Murad describe a number of suitable ingredients and are incorporated by reference herein.

The examples given herein below illustrate the preparation of certain esters of azelaic acid. Only a few of the many possible embodiments that may be anticipated are shown by these examples which are intended to define, in a non-limiting sense, the scope encompassed by the invention. The examples further illustrate the antibacterial and antifungal actions of this compound and demonstrate the complete absence of side effects when the 90% diethyl ester is applied topically to the forearm of healthy volunteers.

Detailed descriptions of the preparation of some azelaic acid esters are given in Examples 1-5.

EXAMPLE 1

Preparation of diethyl azelate (Formula (I), $R_1 = R_2 = C_2 H_5$)

A mixture of azelaic acid (20 g) and 200 proof USP anhydrous ethanol (200 ml) was placed into a 350 ml gas washing bottle. Into this solution anhydrous

hydrogen chloride gas was instilled through the gas inlet of the bottle. The addition of gas was carried out in a chemical fume hood with stirring at room temperature. The gas was bubbled into the solution at a rate such that few if any of the bubbles reached the surface of the solution, as hydrogen chloride is very soluble in alcohols and thus the gas dissolves before escaping the solution. The addition of gas was continued for 2 hours at which point the gas tank was turned off and disconnected. Stirring was continued overnight. The following day the solution was heated to reflux in an open 1 L Erlenmeyer flask and allowed to reflux for 2 hours. This heating had the effect of driving off a large portion of the dissolved hydrogen chloride. The solution was then cooled to room temperature and concentrated under vacuum to produce a clear, slightly yellow oil. This oil was the predominantly the diethyl ester of azelaic acid. The crude diester was dissolved in ethyl acetate and washed several times with a saturated water solution of sodium bicarbonate. The diester was then washed several more times with water until the pH of the wash water was neutral. The semi-purified diester was then vacuum distilled to produce 22 grams of the diester (88% of theoretical).

EXAMPLE 2

Preparation of dipropyl azelate (Formula (I), $R_1 = R_2 = C_3H_7$)

n-Propyl chloride (13.1 ml) was added while stirring to a mixture of sodium bicarbonate (20 g) and azelaid acid (3.75 g) in anhydrous *n*-propanol. After complete addition the mixture was stirred at 40 °C for 90 min. 100 ml of 0.1 N sodium hydroxide in water was added to the reaction mixture and stirring was continued for an additional hour. The alcohol was removed under vacuum and the water/ester mixture was extracted with chloroform (2 X 100 ml). The combined chloroform extracts were dried over anhydrous sodium sulphate and evaporated *in vacuo* to yield the title diester as a colorless oil in 95% yield.

EXAMPLE 3

Preparation of diisobutyl azelate (Formula (I), R1 = R2 = (CH3)2 CH2 CH2)

The compound was prepared essentially as described in Example 1, using isobutyl alcohol instead of ethanol. The product was recovered as a very slightly yellow, clear oil.

EXAMPLE 4

Preparation of dihexyl azelate (Formula (I), $R_1 = R_2 = CH_3 (CH_2)_5$)

The compound was prepared essentially as described in Example 1, using *n*-hexanol instead of ethanol. The product was recovered as a colorless oil.

EXAMPLE 5

Preparation of dihexadecyl azelaic acid (Formula (I), R1 = R2 = CH3 (CH2)15)

The compound was prepared essentially as described in Example 1, using hexadecanoic (palmitoyl) chloride instead of ethanol. The product was recovered as a colorless waxy solid.

EXAMPLE 6

Preparation of Oil-in-Water Emulsion Containing Diethyl-azelate

Preparation of Lipophilic Phase:

100 g of diethyl azelate, 11 g of PEG-30 dipolyhydroxystearate, available from Uniqema, Inc. under the tradename "Arlacel P-135," 20 g of isononyl isononanoate, available from Alzo, Inc. under the tradename, "Wickenol 151," and 20 g of a mixture of hexyldecyl benzoate and butyloctyl benzoate, available from C.P. Hall Company under the tradename, "Hallstar AB" were combined with continuous mixing in a vessel and heated to a temperature of 45 °C until homogeneous. After the mixture was cooled to a temperature of 25 °C, 50 g of cyclomethicone available from Dow Corning under the tradename, "Dow 344 Fluid" and 3.5 g of polysorbate 20 were added thereto with continuous mixing into a glass beaker containing a propeller stirrer until homogeneous.

Preparation of Hydrophilic Phase:

Into a primary glass beaker containing 751 g of deionized water, nitrogen was bubbled therein until the subsequent addition of the lipophilic phase thereto so as to minimize exposure to oxygen. 5 g of PEG-8 caprylic/capric glycerides available from Trivent Inc. under the tradename, "Trivasol BW" was then added thereto with stirring at 25 °C until homogeneous. For aiding in dispersion of the thickener in the formulation, 4 g of carbomer available from B.F. Goodrich, Inc. under the tradename,

"Carbopol Ultrez" was added to 30 g of dimethylisosorbide available from Uniqema, Inc. under the tradename, "Arlasolve DMI" in a separate beaker with hand stirring. Into the dimethylisosorbide mixture was then added 2 g of methylparaben and 1 g of propylparaben with hand stirring until homogeneous to produce a pre-mixture. The pre-mixture was then added to the primary glass beaker with constant stirring until the resulting mixture was homogeneous.

Preparation of Final Composition:

The lipophilic phase was then added to the hydrophilic phase with constant stirring at 25 °C until homogeneous. 2 g of triethanolamine available from Union Carbide under the tradename, "Trolamine 99%" was then added to the resulting mixture with stirring until homogeneous. The final emulsion contains the components as set forth in Table 2:

TABLE 2. Emulsion Components

Chemical Name	Trade Name		% (wt/wt)
Diethyl Azelate			10.0
PEG-30 dipolyhydroxy-stearate	Arlacel P-135	1.1	
Isononyl isononanoate	Wickenol		2.0
Hexyldecyl benzoate and butyloctyl benzoate	Hallstar AB		2.0
Cyclomethicone	Dow 344 Fluid		5.0
Polysorbate 20			0.35
Water	Water		75.15
Carbomer	Carbopol Ultrez		0.40
PEG-8 caprylic/ apric glycerides	Trivasol BW		0.50
Methylparaben	Methylparaben		0.20
Propylparaben	Propylparaben		0.10
Dimethyl isosorbide	Arlasolve DMI		3.0
Triethanolamine	Trolamine 99%		0.2

EXAMPLE 7

Preparation of Oil-in-Water Emulsion Containing Diethyl-azelate

Preparation of Lipophilic Phase:

300 g of dipropylene glycol, 100 g of diethyl azelate, 50 g of isononyl isononanoate, available from Alzo, Inc. under the tradename, "Wickenol 151," and 30 g of a mixture of hexyldecyl benzoate and butyloctyl benzoate, available from C.P. Hall Company under the tradename, "Hallstar AB" were combined with continous mixing in a vessel and heated to a temperature of 45 °C until homogeneous. After the mixture was cooled to a temperature of 25 °C, 50 g of cyclomethicone available from Dow Corning under the tradename, "Dow 344 Fluid" and 3.5 g of polysorbate 20 were added thereto with continuous mixing into a glass beaker containing a propeller stirrer until homogeneous.

Preparation of Hydrophilic Phase:

Into a primary glass beaker containing 313 g of deionized water, 50 g of PEG-60 almond glycerides was then added thereto with stirring at 70 °C and 80 g glycol distearate was added to the mixture while stirring until homogeneous. Into the mixture was then added 2 g. of methylparaben and 1 g of propylparaben with hand stirring until homogeneous.

Preparation of Final Composition:

The lipophilic phase was then added to the hydrophilic phase with constant stirring at 25 °C until homogeneous. 20 g of a mixture of polyacrylamide, C_{13}-C_{14} isoparaffin and Laureth 7 (SEPIGEL 305) is then added and the whole mixed until a thick and homogeneous cream results.

TABLE 3. Emulsion Components

	Chemical Name	Trade Name	% (wt/wt)
	Diethyl Azelate		10.0
	Dipropylene Glycol		30.0
	Isononyl isononanoate	Wickenol	5.0
	Hexyldecyl benzoate and butyloctyl benzoate	Hallstar AB	3.0
	Cyclomethicone	Dow 344 Fluid	5.0
	Polysorbate 20		0.35
	Water	Water	31.35
	Glycol distearate		8.0
	PEG-60 almond glycerides		5.0
	Methylparaben	Methylparaben	0.20
	Propylparaben	Propylparaben	0.10
	Polyacrylamide, C_{13}-C_{14} isoparaffin and Laureth 7	SEPIGEL 305	2.0

EXAMPLE 8

Prepartion of Topical Cream

A skin cream composition containing diethyl azelate is shown in Table 4, and lists the ingredients in the compositions containing diethyl-azelate. The top portion of Table 4 shows the proportions of the base, and the bottom portion shows the constituents and proportions of the additives and all proportions are in units of percent by weight. As shown in Table 4, the base consists of a commercially available moisturizing skin lotion and the additive consists of diethyl-azelate. The base and the additives were mixed thoroughly in a blender to prepare the cream.

TABLE 4. Topical Cream Composition for Diethyl-Azelate

COMPOSITION INGREDIENT NAME	%
A. BASE INGREDIENT	
Lubriderm Moisturizing Lotion sold by Pfizer Healthcare Product Newhaven, Connecticut	90.0
B. ADDITIVES	
Diethyl-Azelate	10.0
TOTAL ADDITIVES	10.0

EXAMPLE 9

Minimum inhibitory concentration of the new azelaic acid ester on Propionibacterium acnes was tested. Serial 2-fold dilutions of 282 grams/l of diethyl azelate were made in 2 ml of the appropriate nutrient broth for this organism. Each tube was then seeded with 0.02 ml of the inoculum (5 day anaerobic culture of propionibacteria in Reinforced Clostridial Medium (Oxoid)). After incubation for an appropriate period (7 days), growth was assessed by eye, and 0.1 ml of the broth showing no visible growth was spread over the surface of a suitable recovery medium to ascertain if viable cells were present. The minimum inhibitory concentration (MIC) was the greatest dilution at which no viable organisms were recovered. MIC of the azelaic acid ester in this experiment was about 85.0 grams/l (0.15 mol/l of diethyl azelate).

EXAMPLE 10

An about 90% solution of diethyl azelate was applied to the forearm of 10 healthy individuals twice daily for a two-week period in an outpatient clinic. No patients complained of burning, irritation, scaling or redness after the cream. Patients returned to the clinic after having used the solution for two weeks for a visual inspection of the forearm area. The examining physician noted no redness, irritation or scaling in the area where the solution had been applied.

REFERENCES

The references listed below are incorporated herein by reference to the extent that they supplement, explain, provide a background for, or teach methodology, techniques, and/or compositions employed herein.

Breathnad AS. Effect of Dicarboxylic Acids, (C6 and C9) on Human Chorosidal Melanomarncellutine, Investigative Optalomolgy & Visual Science 1986; 30: 491-498.

Breatimach AS, Robins EJ, Patzhold HC *et al.*. Effect of Dicarboxylic Acids (C6, C9) on Human Choroidal Melanoma in Cell Culture, Invest Ophthal Vis Sci, 1989; 30: 491-498.

Fitton A and Goa KL. Azelaic acid: A Review of its Pharmacological Properties and Therapeutic Efficacy in Acne and Hyperpigmentary Skin Disorders, Drugs 1991; 41: 180-798.

Fitton A. Azelaic Acid. A review of its Pharmacological Properties and Therapeutic Efficacy in Acne and Hyper-Pigmentation Disorders, Drugs 1991; 41: 780-798.

Galhaup I. Azelaic acid: mode of action at cellular and subcellular levels, In: Breathnach AS, Graupe K, Stingl G. (Eds.) Azelaic acid: A New Therapeutic Agent, Acta Derm Venereol Stockh 1989; 43, (Suppl): 75-82.

Geier G, Haushild T, Bauer R *et al.*. Der Einfluss von Azelainsaure auf das Wachstum von Melanomazelikulturen im Vergleich zu Fibroblastemkulturen, Hautartz 1986; 37: 146-148.

Maddin SA. Comparison of Topical Azelaic Acid 20% Cream and Topical Metronidazole 0.75% cream in the Treatment of Patients with Papulopustular Rosacea, J Am Acad Dermatol 1999; 40: 961-965.

Mortensen PB. Dicarboxylic Acids and the Lipid metabolism, Danish Medical Bulletin, 1984; 31: 121-145.

Nazzaro-Porro M, Passi S, Morpugro G, Breatimach AS. Identification of Tyrosinase Inhibitors in Cultures of Pityrosporum, and their Melanocytotoxic Effect, and Klaus S. N. (Ed.), Pigment Cell, Basel, Karger 1979; 1: 234-243.

Paetzold HC, Breathnach AS, Robins EJ *et al.*. Effect of Dicarboxylic Acids (C6, C9) on a Human Squamous Carcinoma Line in Culture, Histo Histopathol, 1989; 4: 167-171.

Passi S, Picardo M, De Luca C *et al.*. Scavenging Activity of Azelaic Acid on Hydroxyl Radicals In Vitro, Free Rad Res Comm, 1991; 11: 329-339.

Passi S, Picardo M, Nazzaro-Porro M, Breathnach AS *et al.*. Antimitrochondrial Effect of Medium Chain Length (C8 to C13) Dicarboxylic Acids, Biochem Pharmacol 1984; 33: 103-108.

Passi S, Picardo M, Zompetta C *et al.*. Oxyradicals Scavenging Activity of Azelaic Acid in Biological Systems, Free Rad Res Comm, 1991; 15: 17-28.

Passi S. Azelaic Acid--Biochemistry and Metabolism, Acta Derm Veneral, Stockholm, 1989; Supplement (143): 8-13.

Schallreuter KU, Wood JM. Azelaic Acid as a Competitive Inhibitor of Thioredoxin Reductase in Melanoma Cells. Cancer Letters 1987; 36: 297-305.

Stamatidas D, Bulteau-Portois MC, Moszowicz I. Inhibition of 5-□-Reductase Activity in Human Skin by Zinc and Azelaic acid, Br J Dermatol, 1988; 118: 627-632.

Zaffaroni N, Villa R, Silvestro L *et al.*. Cytotoxic Activity of Azelaic Acid Against Human Primary Melanoma Cultures and Established Cell Lines, Anti-Can Res, 1990; 10: 1599-1602.

CLAIMS:

1. A method for treating a skin condition, comprising administering to a patient in need of such treatment a therapeutically effective amount of a dicarboxylic acid ester, or a pharmaceutically acceptable salt thereof, dissolved in a lipophilic medium or a medium essentially free of ethanol and/or isopropanol.

2. The method of claim 1, wherein the dicarboxylic acid ester, or a pharmaceutically acceptable salt thereof, is dissolved in a lipophilic medium.

3. The method of claim 2, wherein the lipophilic medium comprises a triglyceride, an alcohol, a polyol, an amide, an ester, or a propylene glycol ether, or a mixture thereof.

4. The method of claim 1, 2 or 3, wherein the dicarboxylic acid ester, or a pharmaceutically acceptable salt thereof, is dissolved in a medium essentially free of ethanol and/or isopropanol.

5. The method of claim 1, wherein the skin condition is acne, psoriasis, rosacea, aging of the skin, alopecia, solar keratoses, bacterial infection, malignant melanoma, melasma, lentigo maligna, hyperpigmentation, wrinkles, blemishes, lesions of the skin, perioral dermatitis, micoplasma infection, or impetigo.

6. The method of claim 5, wherein the skin condition is acne.

7. The method of claim 5, wherein the skin condition is psoriasis.

8. A method for treating acne or psoriasis, comprising administering to a patient in need of such treatment a therapeutically effective amount of a dicarboxylic acid ester, or a pharmaceutically acceptable salt thereof.

9. The method of claim 1 or 8, wherein the dicarboxylic acid ester, or pharmaceutically acceptable salt thereof, is administered by application to an affected area of skin.

10. A method for treating a skin condition, comprising administering to a patient in need of such treatment a therapeutically effective amount of a dicarboxylic acid ester, or a pharmaceutically acceptable salt thereof, wherein the dicarboxylic acid ester has the formula (I)

$$R_2OOC\text{-}(CH_2)n\text{-}COOR_1 \qquad (I)$$

wherein R_1 and R_2 are each independently hydrogen, a substituted or non-substituted alkyl, aryl, alkylene or arylene group of up to 18 carbon atoms, or a substituted or non-substituted cyclic alkyl, phenalkyl, alkenyl or heteroaryl group,

and wherein

n is an integer from 1-16,

the alkyl, aryl, alkylene and arylene groups are branched or straight chained,

R_1 and R_2 can each independently contain one or more heteroatoms, and

R_1 and R_2 are not simultaneously hydrogen.

11. The method of claim 10, wherein R_1 and R_2 are each independently hydrogen or a substituted or non-substituted alkyl, aryl, alkylene or arylene group of up to 18 carbon atoms.

12. The method of claim 10, wherein n = 5, 7, 9, 10, 11, 12, 13, 14 or 16.

13. The method of claim 12, wherein n = 5, 7, 9, 11 or 13.

14. The method of claim 13, wherein n = 7.

15. The method of claim 10, wherein R_1 and R_2 are each independently a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, hexadecyl, octadecyl, palmityl, stearyl, methoxyethyl, ethoxyethyl, benzyl or nicotninyl group.

16. The method of claim 15, wherein R_1 and R_2 are each independently a methyl, ethyl, propyl, isopropyl, isobutyl, hexyl, hexadecyl, or octadecyl group.

17. The method of claim 15 or 16, wherein R_1 and R_2 are the same.

18. The method of claim 10, wherein R_1 is a methyl, ethyl, propyl, isopropyl, isobutyl, hexyl, hexadecyl, or octadecyl group, and R_2 is hydrogen.

19. The method of claim 10, wherein the dicarboxylic acid ester, or pharmaceutically acceptable salt thereof, is dissolved in a lipophilic medium.

20. The method of claim 19, wherein the lipophilic medium comprises a triglyceride, an alcohol, a polyol, an amide, an ester, or a propylene glycol ether, or a mixture thereof.

21. The method of claim 10, 19 or 20, wherein the dicarboxylic acid ester, or pharmaceutically acceptable salt thereof, is dissolved in a medium essentially free of ethanol and/or isopropanol.

22. The method of claim 10, wherein the skin condition is acne, psoriasis, rosacea, aging of the skin, alopecia, solar keratoses, bacterial infection, malignant melanoma, melasma, lentigo maligna, hyperpigmentation, wrinkles, blemishes, lesions of the skin, perioral dermatitis, micoplasma infection or impetigo.

23. The method of claim 22, wherein the skin condition is acne.

24. The method of claim 22, wherein the skin condition is psoriasis.

25. The method of claim 10, wherein the dicarboxylic acid ester, or pharmaceutically acceptable salt thereof, is administered by application to an affected area of skin.

26. The method in accordance with any of claims 1-8 and 10-24, wherein the dicarboxylic acid ester, or pharmaceutically acceptable salt thereof, is administered orally, parenterally, rectally, nasally, buccally, transdermally, *via* an implanted reservoir, or topically.

27. The method in accordance with any of claim 9, 25 or 26, wherein the dicarboxylic acid ester, or pharmaceutically acceptable salt thereof, is administered topically in an ointment, crème, lotion, paste, gel, drops, spray, liquid, shampoo, or transdermal patch.

28. A method for treating a skin condition, comprising administering to a patient in need of such treatment a therapeutically effective amount of a geminal diol or a pharmaceutically acceptable salt thereof, said geminal diol having the formula (II)

$$HO\text{-}(CH_2)n\text{-}OH \qquad (II)$$

wherein n is an integer from 1-16.

29. A method for treating a skin condition, comprising administering to a patient in need of such treatment a therapeutically effective amount of an omega-hydroxy carboxylic acid or a pharmaceutically acceptable salt thereof, said omega-hydroxy carboxylic acid having the formula (III)

$$HO\text{-}(CH_2)n\text{-}COOR \qquad (III)$$

wherein R is a substituted or non-substituted alkyl, aryl, alkylene or arylene group of up to 18 carbon atoms and n is an integer from 1-16, and wherein the alkyl, aryl, alkylene and arylene groups are branched or straight chained and R can contain one or more heteroatoms.

30. The method of claim 29 wherein R is selected from the group consisting of a methyl group, ethyl group, propyl group, isopropyl group, isobutyl group, hexyl group, hexadecyl group and octadecyl group.

31. The method of claim 28 or 29 wherein n = 5, 7, 9, 10, 11, 12, 13, 14 or 16.

32. The method of claim 31 wherein n = 5, 7, 9, 11 or 13.

33. The method of claim 32 wherein n = 7.

34. The method of claim 28 or 29, wherein the skin condition is acne, psoriasis, rosacea, aging of the skin, alopecia, solar keratoses, bacterial infection, malignant melanoma, melasma, lentigo maligna, hyperpigmentation, wrinkles, blemishes, lesions of the skin, perioral dermatitis, micoplasma infection, or impetigo.

35. The method of claim 34, wherein the skin condition is acne.

36. The method of claim 34, wherein the skin condition is psoriasis.

37. The method in accordance with any of claims 28-36, wherein the geminal diol, omega-hydroxy carboxylic acid, or pharmaceutically acceptable salt thereof, is administered orally, parenterally, rectally, nasally, buccally, transdermally, via an implanted reservoir, or topically.

38. The method in accordance with any of claim 37, wherein the geminal diol, omega-hydroxy carboxylic acid, or pharmaceutically acceptable salt thereof, is administered topically in an ointment, crème, lotion, paste, gel, drops, spray, liquid, shampoo, or transdermal patch.

39. A pharmaceutical composition for treating a skin condition, comprising a therapeutically effective amount of a dicarboxylic acid ester, or a pharmaceutically acceptable salt thereof, dissolved in a lipophilic medium or a medium essentially free of ethanol and/or isopropanol.

40. The pharmaceutical composition of claim 39, wherein the dicarboxylic acid ester, or a pharmaceutically acceptable salt thereof, is dissolved in a

lipophilic medium.

41. The pharmaceutical composition of claim 40, wherein the lipophilic medium comprises a triglyceride, an alcohol, a polyol, an amide, an ester, or a propylene glycol ether, or a mixture thereof.

42. The pharmaceutical composition of claim 39, 40 or 41, wherein the dicarboxylic acid ester, or a pharmaceutically acceptable salt thereof, is dissolved in a medium essentially free of ethanol and/or isopropanol.

43. A pharmaceutical composition for treating a skin condition, comprising a therapeutically effective amount of a dicarboxylic acid ester, or a pharmaceutically acceptable salt thereof, wherein the dicarboxylic acid ester has the formula (I)

$$R_2OOC\text{-}(CH_2)n\text{-}COOR_1 \qquad (I)$$

wherein R_1 and R_2 are each independently hydrogen, a substituted or non-substituted alkyl, aryl, alkylene or arylene group of up to 18 carbon atoms, or a substituted or non-substituted cyclic alkyl, phenalkyl, alkenyl or heteroaryl group,

and wherein

n is an integer from 1-16,

the alkyl, aryl, alkylene and arylene groups are branched or straight chained,

R_1 and R_2 can each independently contain one or more heteroatoms, and

R_1 and R_2 are not simultaneously hydrogen.

44. The pharmaceutical composition of claim 43, wherein R_1 and R_2 are each independently hydrogen or a substituted or non-substituted alkyl, aryl, alkylene or arylene group of up to 18 carbon atoms.

45. The pharmaceutical composition of claim 43, wherein n = 5, 7, 9, 10, 11, 12, 13, 14 or 16.

46. The pharmaceutical composition of claim 45, wherein n = 5, 7, 9, 11 or 13.

47. The pharmaceutical composition of claim 46, wherein n = 7.

48. The pharmaceutical composition of claim 43, wherein R_1 and R_2 are each independently a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, hexadecyl, octadecyl, palmityl, stearyl, methoxyethyl, ethoxyethyl, benzyl or nicotninyl group.

49. The pharmaceutical composition of claim 48, wherein R_1 and R_2 are each independently a methyl, ethyl, propyl, isopropyl, isobutyl, hexyl, hexadecyl, or octadecyl group.

50. The pharmaceutical composition of claim 48 or 49, wherein R_1 and R_2 are the same.

51. The pharmaceutical composition of claim 43, wherein R_1 is a methyl, ethyl, propyl, isopropyl, isobutyl, hexyl, hexadecyl, or octadecyl group, and R_2 is hydrogen.

52. The pharmaceutical composition of claim 43, wherein the dicarboxylic acid ester is dissolved in a lipophilic medium.

53. The pharmaceutical composition of claim 52, wherein the lipophilic medium comprises a triglyceride, an alcohol, a polyol, an amide, an ester, or a propylene glycol ether, or a mixture thereof.

54. The pharmaceutical composition of claim 43, 52 or 53, wherein the dicarboxylic acid ester is dissolved in a medium essentially free of ethanol and/or isopropanol.

55. The pharmaceutical composition in accordance with any of claims 39-54, wherein the pharmaceutical composition is in a dosage form for

administering orally, parenterally, rectally, nasally, buccally, transdermally, via an implanted reservoir, or topically.

56. The pharmaceutical composition of claim 55, wherein the dosage form is an ointment, crème, lotion, paste, gel, drops, spray, liquid, shampoo, or transdermal patch, for topical administration.

57. A pharmaceutical composition for treating a skin condition, comprising a therapeutically effective amount of a geminal diol, or a pharmaceutically acceptable salt thereof, said geminal diol having the formula (II)

$$HO\text{-}(CH_2)n\text{-}OH \qquad (II)$$

wherein n is an integer from 1-16.

58. The pharmaceutical composition of claim 57, wherein the geminal diol is dissolved in a lipophilic medium or a medium essentially free of ethanol and/or isopropanol.

59. A pharmaceutical composition for treating a skin condition, comprising a therapeutically effective amount of an omega-hydroxy carboxylic acid, or a pharmaceutically acceptable salt thereof, said omega-hydroxy carboxylic acid having the formula (III)

$$HO\text{-}(CH_2)n\text{-}COOR \qquad (III)$$

wherein R is a substituted or non-substituted alkyl, aryl, alkylene or arylene group of up to 18 carbon atoms and n is an integer from 1-16, and wherein the alkyl, aryl, alkylene and arylene groups are branched or straight chained and R can contain one or more heteroatoms.

60. The pharmaceutical composition of claim 59, wherein R is selected from the group consisting of a methyl group, ethyl group, propyl group, isoprpyl group, isobutyl group, hexyl group, hexadecyl group and octadecyl group.

61. The pharmaceutical composition of claim 59, wherein the omega-hydroxy carboxylic acid is dissolved in a lipophilic medium or a medium essentially free of ethanol and/or isopropanol.

62. The method of claim 57 or 59, wherein n = 5, 7, 9, 10, 11, 12, 13, 14 or 16.

63. The method of claim 62, wherein n = 5, 7, 9, 11 or 13.

64. The method of claim 63 wherein n = 7.

65. The pharmaceutical composition in accordance with any of claims 57-64, wherein the pharmaceutical composition is in a dosage form for administering orally, parenterally, rectally, nasally, buccally, transdermally, via an implanted reservoir, or topically.

The pharmaceutical composition of claim 65, wherein the dosage form is an ointment, crème, lotion, paste, gel, drops, spray, liquid, shampoo, or transdermal patch, for topical administration.