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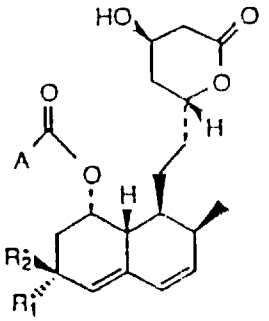
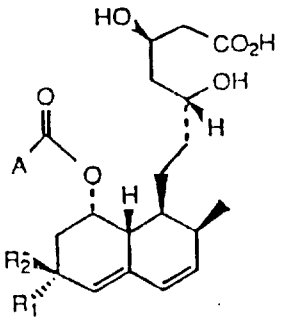
METHOD FOR TOPICAL TREATMENT
OF SKIN DISEASES

Abstract

Compounds of formula I and II



I



II

wherein R_1 is hydrogen and R_2 is hydroxy or R_1 is methyl and R_2 is hydrogen; A is alkyl; cycloalkyl; alkenyl; alkyl substituted with trifluoromethyl; phenyl; halophenyl; phenyl-C_{1-3} alkyl; phenyl-C_{1-3} alkyl substituted on the phenyl with 1 to 3 substituents selected from the group consisting of halo, C_{1-3} alkyl, or C_{1-3} alkoxy; or A is

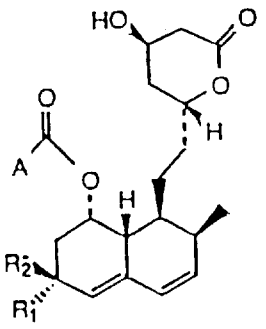
$$R_3O(CH_2)_n-C-(CH_3)(R_4)-$$

wherein R_3 is hydrogen or (C_{1-5} alkyl)C-(O)-, R_4 is hydrogen or methyl, and n is 1 to 5; or a pharmaceutically acceptable salt, C_{1-4}-alkyl ester, acetylamino-C_{1-4} alkyl ester, phenyl-C_{1-4}-alkyl ester, dimethylamino-C_{1-4} alkyl ester, or a α-monoglyceride of a compound of formula II are useful in the treatment of hyperproliferative diseases, suh as psoriasis.

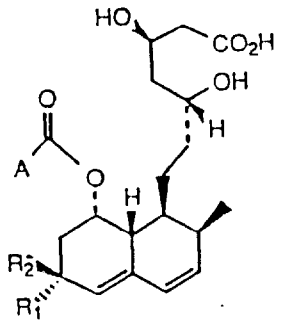
29006

METHOD FOR TOPICAL TREATMENT OF SKIN DISEASES

The present invention is concerned with the use of compounds of the formulas



I



II

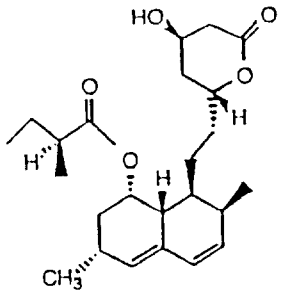
wherein R_1 is hydrogen and R_2 is hydroxy; or R_1 is methyl and R_2 is hydrogen; A is alkyl; cycloalkyl; alkenyl; alkyl substituted with trifluoromethyl; phenyl; halophenyl; phenyl C_{1-3} alkyl; phenyl-C_{1-3} alkyl substituted on the phenyl with 1 to 3 substituents selected from the group consisting of halo, C_{1-3} alkyl, and C_{1-3} alkoxy; or A is

$$R_3O(CH_2)_n\text{-}C\text{-}(CH_3)(R_4)\text{-}$$

wherein R_3 is hydrogen or (C_{1-5} alkyl)C-(O)-, R_4 is hydrogen or methyl, and n is 1 to 5; and pharmaceutically acceptable salts, C_{1-4}-alkyl esters, acetylamino-C_{1-4}-alkyl esters, phenyl C_{1-4}-alkyl esters; dimethylamino-C_{1-4} alkyl esters or

α-monoglycerides of the compounds of formula II.

Preferred compounds of the formulas I and II are compounds of formulas



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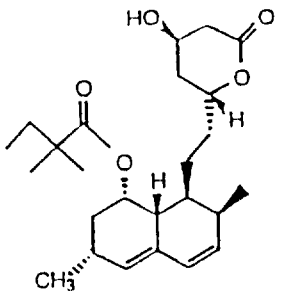

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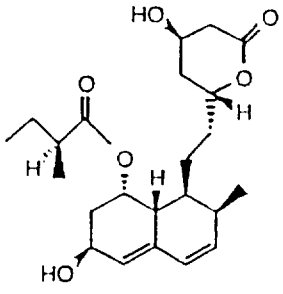

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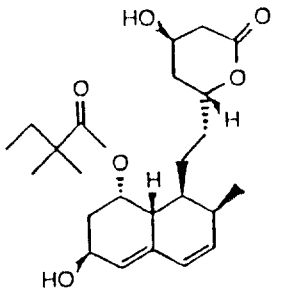

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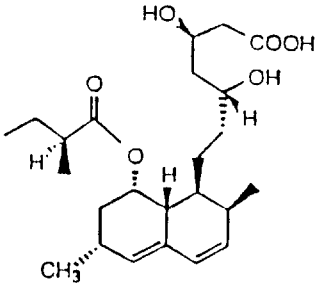

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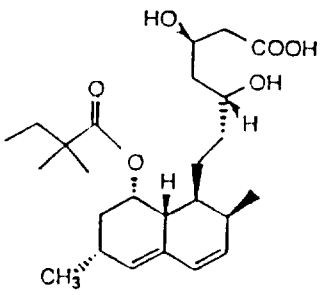

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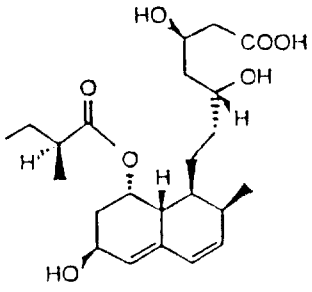

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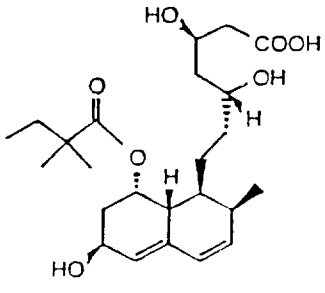

X

It has been unexpectedly found that the compounds of formulas I and II and the above-identified esters and monoglycerides of the compounds of formula II are useful in the treatment of hyperproliferative skin diseases, such as psoriasis, basal cell carcinomas, squamous cell carcinomas, keratosis, and disorders of keratinization. These compounds may be administered either orally or topically.

Pharmaceutical compositions for topical applications containing a compound of the formula I and II and the above-identified esters and monoglycerides of the compounds of formula II are novel and are also an object of the present invention.

Compounds of formulas I and II wherein R_1 is methyl and A is as described above may be prepared by methods disclosed in U.S. Patent 4,444,784 and 4,450,171.

Compounds of formula I are converted into the compound of formula II in a manner analogous to that discussed in U.S. Patent 4,444,784.

Compounds of formulas V, VI, IX and X may be prepared by known methods discussed in U.S. Patent No. 4,346,227.

As used herein, the term "psoriasis" refers to a hyperproliferative skin disease which alters the skin's regulatory mechanisms. In particular, lesions are formed which involve primary and secondary alterations in epidermal proliferation, inflammatory responses of the skin, and an expression of regulatory molecules such as lymphokines and inflammatory factors. Psoriatic skin is morphologically characterized by an increased turnover of epidermal cells, thickened epidermis, abnormal keratinization, inflammatory cell infiltrates into the dermis layer and polymorphonuclear leukocyte infiltration into the epidermis layer resulting in an increase in the basal cell cycle. Additionally,

hyperkeratotic and parakeratotic cells are present.

The terms "keratosis," "basal cell carcinomas" and "disorders of keratinization" refer to hyperproliferative skin diseases in which the regulatory mechanisms for the proliferation and differentiation of normal skin cells are disrupted.

The compounds of formulas I an II and the above identified esters and monoglycerides of the compounds of formula II are active as skin hyperproliferation antagonists, that is, as agents which decrease the proliferation of human keratinocytes. The compounds further antagonize alterations in the differentiation of keratinocytes. Accordingly, the compounds are useful as agents for the treatment of hyperproliferative skin diseases such as psoriasis, basal cell carcinomas, disorders of keratinization and keratosis.

As used herein the term "halo" means chloro, fluoro, bromo, or iodo.

As used herein the term "alkyl" denotes a straight or branched chain saturated hydrocarbon having 1 to 10 carbon atoms such as methyl, ethyl, propyl, isopropyl and the like.

The term "cycloalkyl" denotes a cycloalkyl having 3 to 10 carbon atoms such as cyclopropyl, cyclobutyl, and the like.

The term "alkenyl" denotes a straight or branched chain alkenyl having 2 to 10 carbon atoms such as ethenyl, propenyl and the like.

The term "alkyl substituted with trifluoromethyl" denotes a C_{1-10} straight or branched chain alkyl having

one hydrogen replaced by trifluoromethyl.

The term "halophenyl" denotes a phenyl substituted with up to three halogens.

The term "phenyl C_{1-3} alkyl" denotes an alkyl having 1-3 carbon atoms and one of whose hydrogens is replaced by a phenyl.

In the formulas presented herein, the various substituents are illustrated as joined to the carbon framework by one of the following notations: a tapered line (◄) indicates a substituent which is above the plane of the molecule (ß-orientation) and a dotted line (▪▪▪) or (---) indicates a substituent which is below the plane of the molecule (α-orientation).

Especially preferred of the compounds of formula I is the compound of the formula III which is referred to herein as mevinolin; and the compound of the formula IV which is referred to herein as synvinolin.

The compounds of formulas III and IV are known and can be with known methods, such as those described in U.S. Patent No. 4,346,227.

The compounds of formulas I and II and the above identified esters and monoglycerides of the compounds of formula II can be administered orally, for the treatment of hyperproliferative skin diseases such as psoriasis, basal cell carcinomas, squamous cell carcinomas, disorders of keratinization and keratosis to warm-blooded animals which need such treatment. While dosages may vary depending upon the severity of the disease, these compounds can be administered orally to the adult human in dosages that are in the range of about 10 to 80 milligrams per day and preferably about 10-50 milligrams per day for the treatment

of hyperproliferative skin diseases such as psoriasis, basal cell carcinomas, squamous cell carcinomas, disorders of keratinization and keratosis.

The compounds of formulas I and II can be administered topically, for treatment of hyperproliferative skin diseases, such as psoriasis, basal cell carcinomas, squamous cell carcinomas, disorders of keratinization and keratosis to warm blooded animals which need such treatment. While dosages may vary depending upon the severity of the disease, these compounds can be administered topically in dosages that are about 1 to about 200 micrograms per gram of topical formulation per day for the treatment of such diseases, preferably about 1 to about 50 micrograms per gram of topical formulation per day.

The useful activity of compounds of formulas I and II and the above identified esters and monoglycerides of the compounds of formula II as agents for the treatment of hyperproliferative skin diseases can be demonstrated by the ability of these compounds to inhibite the keratinocyte proliferation in cell cultures of keratinocytes obtained from human neonatal foreskins. The results are compiled in Table 1 below:

TABLE 1

INHIBITION OF COMPOUNDS OF FORMULA I on KERATINOCYTE PROLIFERATION

Compound	Dosage of Compound (M)	Percent Inhibition on Keratinocyte Proliferation	Standard Deviation
1. ETOH Control		0.00	24.48
2. Mevinolin	10^{-10}	23.2	26.7
	10^{-8}	28.9	17.57
	10^{-7}	38.6	12.82
	10^{-6}	84.21	14.51
3. Synvinolin	10^{-10}	0.00	24.08
	10^{-8}	11.17	26.42
	10^{-7}	33.60	26.34
	10^{-6}	62.06	24.31

Each compound is tested in triplicate, at each concentration.

The foregoing results evidence that compounds of formula I at a dosage of 10^{-6}M inhibit keratinocyte cell proliferation at a rate greater than 50% without toxicity to the cells. For example, mevinolin at this dosage inhibits 84.21% of keratinocyte proliferization and synvinolin inhibits 62.06% of keratinocyte proliferization at this dosage.

These data indicate that the compounds of formula I restrain the proliferation of human keratinocyte cells in vitro, without toxicity to the cells. From these results it can be seen that each of the tested compounds is useful as an agent in the treatment of hyperproliferative skin diseases such as psoriasis.

For the manufacture of oral dosage forms compounds of formulas I and II and the above-identified esters and monoglycerides of compounds of formula II may be incorporated in capsules, tablets and the like with pharmaceutically acceptable carrier materials.

Illustrative of the pharmaceutically acceptable carrier materials which may be incorporated into capsules, and the like are the following: a binder such as gum tragacanth, acacia, corn starch, or gelatin; an excipient such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, algenic acid, and the like; a lubricant such as magnesium stearate, a sweetening agent such as sucrose, lactose, or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. Various other materials may be present as coating or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar, or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye, and a flavoring such as cherry or orange flavor.

A preferable formulation for an oral dosage of the compound of Formulas I and II in capsule form is presented in Example 1 below:

Example 1

Oral dosage formulation (capsule) for Compounds of Formulas I-X.

1.	Compound of Formula I or II,	20 milligrams
2.	Lactose	150 milligrams
3.	Starch	30 milligrams
4.	Talc	20 milligrams

Manufacturing Process

A. Mix 1 with a portion of 2.

B. Add 3 and 4, and mix.

C. Add the remainder of 2, mix thoroughly, and pass through a suitable mill. Capsules are filled with the composition thus prepared.

As used herein, the term "topical" denotes the use of the active ingredient, incorporated in a suitable pharmaceutical carrier, and applied at the site of inflammation for the exertion of local action. Accordingly, the topical compositions include those pharmaceutical forms in which the compound is applied externally by direct contract with the skin. The topical dosage forms comprise gels, creams, lotions, ointments, powders, aerosols and other conventional forms for applying medications to the skin obtained by admixing the compounds of formula I with known pharmaceutical topical carrier materials. In addition to the application to the skin, the topical compositions of this invention can also be employed in the treatment of inflammations of mucous membranes, where such membranes are accessible to topical application of medication. For example, the topical composition can be applied to the mucous lining of the mouth or lower colon.

A preferable formulation for a topical dosage of the compounds of Formulas I or II is presented in Example 2 below:

Example 2

Preferred Formulation for Topical Dosage of Compounds of Formulas I or II

1.	Compound of Formula I or II,	10.0 micrograms
2.	Stearyl alcohol	4.0 g
3.	Cetyl alcohol	4.0 g
4.	Mineral oil	3.0 g
5.	Polysorbate 60	4.5 g
6.	Sorbitan stearate	4.5 g
7.	Propylene glycol	10.0 g
8.	Methyl paraben	0.18 g
9.	Propyl paraben	0.02 g
10.	Water	q.s. to 100.00 g

Manufacturing Process

A. Heat 2 through 6 to 80°C, which melts all ingredients (oil phase).
B. Dissolve 1 in oil phase.
C. Heat 7 and 10 to 90°C (aqueous phase).
D. Dissolve 8 and 9 in aqueous phase.
E. Add aqueous phase to the oil phase and stir rapidly to form emulsion.
F. Cool slowly to 50°C to allow to congeal.
G. Continue stirring slowly to room temperature.

CLAIMS:

1. A method for treating a hyperproliferative skin disease in a patient in need of such treatment comprising:

administering an antihyperproliferatively effective amount of mevinolin or synvinolin.

2. The method of claim 1 wherein the compound is orally administered.

3. The method of Claim 2 wherein the dosage range of the compound is about 10 to about 80 milligrams per day.

4. The method of Claim 1 wherein the compound is administered topically.

5. The method of Claim 4 wherein the dosage range of the compound is about 1 to about 200 micrograms per gram of a composition.

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