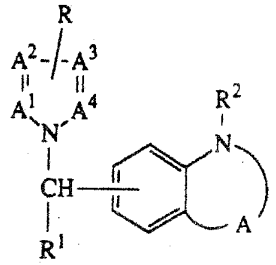
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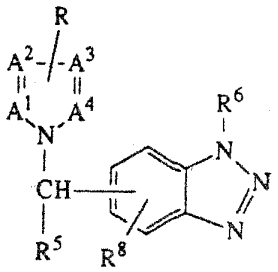
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ABSTRACT

The present invention concerns a pharmaceutical or cosmetical composition comprising an inert carrier, an effective amount of retinoic acid or a derivative thereof, or a stereochemically isomeric form thereof and an effective amount of a compound of formula:



(I) or



(II)

an acid addition salt thereof or a stereochemically isomeric form thereof. The use for the manufacture for treating subjects suffering from disorders which are characterized by an increased proliferation and/or abnormal differentation of normal, preneoplastic or neoplastic epithelial cells the growth of which is sensitive to the action of retinoids is also disclosed.

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COMPOSITIONS FOR TREATING EPITHELIAL DISORDERS

Retinoids, in particular retinoic acid and its derivatives, are substances which are known to have a broad spectrum of biological activity. More specifically, these substances affect the differentiation, maintenance and proliferation of various cell types. The ability of retinoids, such as, all-*trans*-retinoic acid, 13-*cis*-retinoic acid, and their derivatives to modulate differentiation in several cell types, whether they are of epithelial or mesenchymal origin, is extensively studied and reviewed in J. Clin. Chem. Clin. Biochem., 26, 479-488 (1983); Pharmacological Reviews, 36, 935-1005 (1984) and Arch. Dermatol., 117, 160-180 (1981).

It is known that certain retinoids, particularly the retinoic acids, are used topically for treatment of acne as set forth in U.S. Patent No. 3,729,568. Other known uses of retinoic acid were reviewed in the Journal of American Academy of Dermatology, 4, 505-516 (1981) and the Journal of Medical Chemistry, 25, 1269-1277 (1982) and include, in addition to acne treatment, treatment of senile comedones, nevus comedonicus, linear verrucous nevus, plantar warts, pseudofolliculitis, keratoacanthoma, solar keratosis of extremities, callosities, keratosis palmaris et plantaris, Darier's disease, ichthyosis, psoriasis, acanthosis nigricans, lichen planus, molluscum contagiosum, reactive perforating collagenosis, melasma, corneal epithelial abrasion, Fox-Fordyce disease, cutaneous metastatic melanoma and keloids or hypertrophic scars.

Retinoids such as, all-*trans*-retinoic acid, 13-*cis*-retinoic acid and their derivatives, have also been used in the treatment of carcinomas.

There are however a number of drawbacks associated with the therapeutic applications of retinoids. The topical applications of retinoids on the one hand often cause significant irritation and peeling due to the relatively high concentrations of retinoid which have to be applied. Systemic applications on the other hand are limited by the toxicity and rapid degradation of the administered retinoids.

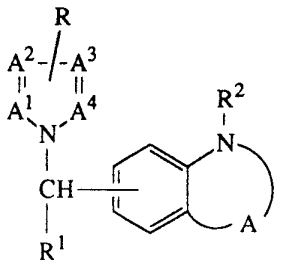
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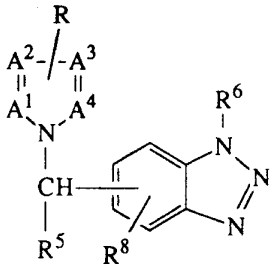
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The compositions of the invention overcome the problems associated with art known retinoid therapy by suppressing the metabolism of endogenously or exogenously administered retinoic acid.

The present invention concerns compositions comprising an inert carrier, an effective amount of a retinoic acid or a derivative thereof, or a stereochemically isomeric form thereof and an effective amount of a compound of formula



(I) or



(II)

a pharmaceutically acceptable acid addition salt thereof or a stereochemically isomeric form thereof, wherein

R, R^1, R^2, $-A^1=A^2-A^3=A^4-$ and A in formula (I) have the following meaning

$-A^1=A^2-A^3=A^4-$ is a bivalent radical having the formula

-CH=N-CH=CH- (x);

-CH=N-CH=N- (y); or

-CH=N-N=CH- (z);

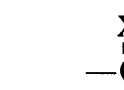
R is hydrogen or C_{1-6}alkyl;

R^1 is hydrogen; C_{1-10}alkyl; C_{3-7}cycloalkyl; Ar^1 or Ar^1-C_{1-6}alkyl;

R^2 is hydrogen; C_{3-7}cycloalkyl; Ar^1; C_{1-10}alkyl; C_{1-6}alkyl substituted with Ar^1 or C_{3-7}cycloalkyl; hydroxy; C_{1-10}alkyloxy; C_{1-6}alkyloxy substituted with Ar^1 or C_{3-7}cycloalkyl; C_{3-6}alkenyloxy optionally substituted with Ar^2; C_{3-6}alkynyloxy optionally substituted with Ar^2; or Ar^1-oxy;

A is a bivalent radical having the formula

$-CR^3=N-$ (a) or



(b),

wherein the carbon atom in the bivalent radical (a) and (b) is connected to $-NR^2$;

said R^3 being hydrogen; halo; C_{1-4}alkyl substituted with up to 4 halo atoms; C_{3-7}cycloalkyl; Ar^1; quinolinyl; indolinyl; C_{1-10}alkyl; C_{1-6}alkyl substituted with Ar^1, C_{3-7}cycloalkyl, quinolinyl, indolinyl or hydroxy; C_{1-10}alkyloxy; C_{1-6}alkyloxy substituted with Ar^1 or C_{3-7}cycloalkyl; C_{2-6}alkenyl optionally substituted with Ar^1;

Ar^2-oxy; C_{1-6}alkyloxycarbonyl; carboxyl; C_{1-6}alkylcarbonyl; Ar^1-carbonyl or Ar^1-(CHOH)-;

said X being O or S;

said R^4 being hydrogen, C_{1-6}alkyl or Ar^2-C_{1-6}alkyl;

wherein Ar^1 is phenyl, substituted phenyl, pyridinyl, aminopyridinyl, imidazolyl, thienyl, halothienyl, furanyl, halofuranyl or thiazolyl; and Ar^2 is phenyl or substituted phenyl; said substituted phenyl in Ar^1 and Ar^2 being phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, amino, mono- and di(C_{1-6}alkyl)amino, nitro, carboxyl, formyl and C_{1-6}alkyloxycarbonyl; and wherein

R, R^5, R^6, R^7 and -A^1=A^2-A^3=A^4- in formula (II) have the following meaning

-A^1=A^2-A^3=A^4- is a bivalent radical having the formula

-CH=N-CH=CH- (x);

-CH=N-CH=N- (y); or

-CH=N-N=CH- (z);

R is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen; C_{1-10}alkyl; C_{3-7}cycloalkyl; Ar^3; Ar^4-C_{1-6}alkyl; C_{2-6}alkenyl or C_{2-6}alkynyl;

R^6 is hydrogen; C_{1-10}alkyl optionally substituted with Ar^3, C_{3-7}cycloalkyl, hydroxy or C_{1-6}alkyloxy; Ar^3; C_{2-6}alkenyl; C_{2-6}alkynyl; C_{3-7}cycloalkyl; bicyclo-[2.2.1]heptan-2-yl; 2,3-dihydro-1H-indenyl; 1,2,3,4-tetrahydronaphthalenyl; or a radical of formula OR^7,

R^7 is hydrogen; C_{2-6}alkenyl optionally substituted with Ar^4; C_{2-6}alkynyl; pyrimidinyl, di(Ar^4)methyl; 1-C_{1-4}alkyl-4-piperidinyl; or C_{1-10}alkyl optionally substituted with halo, hydroxy, C_{1-6}alkyloxy, amino, mono- and di(C_{1-6}alkyl)-amino, trifluoromethyl, carboxyl, C_{1-6}alkyloxycarbonyl, Ar^3, Ar^4-O-, Ar^4-S-, C_{3-7}cycloalkyl, 2,3-dihydro-1,4-benzodioxinyl, 1H-benzimidazolyl, C_{1-4}alkyl substituted 1H-benzimidazolyl, (1,1'-biphenyl)-4-yl or with 2,3-dihydro-2-oxo-1H-benzimidazolyl;

R^8 is hydrogen, nitro, amino, mono- and di(C_{1-6}alkyl)amino, halo, C_{1-6}alkyl, hydroxy or C_{1-6}alkyloxy;

wherein Ar^3 is phenyl, substituted phenyl, naphthalenyl, pyridinyl, aminopyridinyl, imidazolyl, triazolyl, thienyl, halothienyl, furanyl, C_{1-6}alkylfuranyl, halofuranyl or thiazolyl; Ar^4 is phenyl, substituted phenyl or pyridinyl, said substituted phenyl in Ar^3 and Ar^4 being phenyl substituted with up to 3 substituents each independently selected from halo, hydroxy, hydroxymethyl, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, formyl, (hydroxyimino)methyl, cyano, amino, mono-

and di(C_{1-6}alkyl)amino and nitro. Preferably said substituted phenyl is phenyl substituted with one or two substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy and trifluoromethyl.

As used in the foregoing definitions the term halo is generic to fluoro, chloro, bromo and iodo; the term "C_{1-6}alkyl" is meant to include straight chained and branched saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like; "C_{1-10}alkyl" is meant to include C_{1-6}alkyl radicals, as defined hereinabove, and the higher homologs thereof having from 7 to 10 carbon atoms; the term "C_{3-7}cycloalkyl" is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. "C_{2-6}alkenyl" defines straight chained and branched hydrocarbon radicals containing one double bond having from 2 to 6 carbon atoms such as, for example, ethenyl, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl and the like; "C_{2-6}alkynyl" defines straight chained and branched hydrocarbon radicals containing one triple bond and having from 2 to 6 carbon atoms such as, for example, 2-propynyl, 2-butynyl, 3-butynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl and the like; and when a C_{2-6}alkenyl or a C_{2-6}alkynyl is substituted on a heteroatom, then the carbon atom of said C_{2-6}alkenyl or said C_{2-6}alkynyl connected to said heteroatom preferably is saturated.

It is to be understood that the



moiety in formula (I) and the



moiety in formula (II),

both hereinafter referred as the 1H-azol-1-ylmethyl moiety, may be substituted on either the 4, 5, 6 or 7 position of the benzimidazole or benzotriazole heterocyclic ring, preferably on the 5 or 6 position, with the 5 position being preferred.

It is evident that the compounds of formula (I) may also contain in their structure a tautomeric system and consequently these compounds can be present in each of their tautomeric forms.

Particular compounds are those compounds of formula (I) wherein the 1H-azol-1-ylmethyl moiety is substituted on either the 5 or 6 position of the benzimidazole ring; and/or R is hydrogen; and/or R^1 is hydrogen; C_{1-6}alkyl; C_{3-7}cycloalkyl; phenyl; substituted phenyl; thienyl or furanyl optionally substituted with halo; and/or R^2 is hydrogen; C_{3-7}cycloalkyl; phenyl; substituted phenyl; pyridinyl; C_{1-6}alkyl optionally monosubstituted with phenyl, C_{3-7}cycloalkyl, pyridinyl or thienyl; hydroxyl, C_{1-6}alkyloxy optionally monosubstituted with phenyl, pyridinyl, thienyl or C_{3-6}cycloalkyl; C_{3-6}alkenyloxy optionally monosubstituted with phenyl; or C_{3-6}alkynyloxy; and/or R^3 is hydrogen; C_{1-4}alkyl substituted with up to 4 halo atoms; C_{3-7}cycloalkyl; phenyl; substituted phenyl; imidazolyl; thiazolyl; thienyl; furanyl; quinolinyl; pyridinyl optionally substituted with amino, C_{1-10}alkyl; C_{1-5}alkyl optionally monosubstituted with phenyl, pyridinyl, imidazolyl, thienyl, indolyl or hydroxyl; C_{1-4}alkyloxy optionally monosubstituted with phenyl; C_{2-6}alkenyl optionally monosubstituted with pyridinyl, furanyl, imidazolyl or phenyl; carboxyl; C_{1-4}alkyloxycarbonyl; phenylcarbonyl; or hydroxy and phenylmethyl; and/or R^4 is hydrogen or phenylC_{1-4}alkyl.

Other particular compounds are those compounds of formula (II) wherein the 1H-azol-1-ylmethyl moiety is substituted on either the 5 or 6 position of the benzotriazole ring; and/or R is hydrogen; and/or R^5 is hydrogen; C_{1-6}alkyl; phenyl; substituted phenyl; C_{3-7}cycloalkyl; thienyl or furanyl optionally substituted with halo; and/or R^6 is hydrogen; C_{1-6}alkyl; C_{3-6}alkenyl; C_{3-6}alkynyl; C_{3-7}cycloalkyl; phenyl; substituted phenyl; bicylo[2.2.1]heptan-2-yl; 2,3-dihydro-1H-indenyl; 1,2,3,4-tetrahydronaphthalenyl; C_{1-6}alkyl monosubstituted with phenyl, substituted phenyl, naphthalenyl, thienyl, furanyl, C_{1-4}alkylfuranyl, C_{3-7}cycloalkyl, hydroxy, C_{1-4}alkyloxy; or R^6 is a radical $-OR^7$ with R^7 being hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, phenylC_{3-6}alkenyl, C_{3-6}alkynyl, pyrimidinyl, diphenylmethyl, (1-C_{1-4}alkyl-4-piperidinyl), C_{1-6}alkyl substituted with halo, hydroxy, amino, mono- or di(C_{1-6}alkyl)amino, trifluoromethyl, carboxyl, C_{1-6}alkyloxycarbonyl, phenyl, substituted phenyl, thienyl, furanyl, C_{1-4}alkylfuranyl, pyridinyl, phenoxy, phenylthio, 2,3-dihydro-1,4-benzodioxinyl, 1H-benzimidazolyl, C_{1-4}alkyl substituted 1H-benzimidazolyl, (1,1'-biphenyl)-4-yl or 2,3-dihydro-2-oxo-1H-benzimidazolyl; and/or R^8 is hydrogen.

More particular compounds are those particular compounds of formula (I) wherein R^1 is hydrogen, C_{1-6}alkyl, phenyl, substituted phenyl, thienyl or furanyl; R^2 is hydrogen, C_{1-6}alkyl, or C_{1-4}alkyl substituted with phenyl; R^3 is hydrogen, C_{1-6}alkyl, phenyl, pyridinyl, C_{1-6}alkyl, C_{1-6}alkyl monosubstituted with phenyl or C_{2-6}alkenyl optionally monosubstituted with furanyl or phenyl; and R^4 is hydrogen.

Other more particular compounds of the present invention are those particular compounds of formula (II) wherein R^5 is hydrogen, C_{1-6}alkyl, phenyl, substituted phenyl, thienyl or furanyl; R^6 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyl substituted with phenyl, or a radical of formula -OR^7 with R^7 being hydrogen or C_{1-6}alkyl.

Preferred compounds are those particular compounds of formula (I) wherein R^1 is C_{1-4}alkyl, phenyl, phenyl substituted with one or two halo, C_{1-4}alkyl or C_{1-4}alkyloxy substituents, or thienyl; R^2 is hydrogen or C_{1-4}alkyl; and R^3 is hydrogen or C_{1-4}alkyl.

Other preferred compounds are those particular compounds of fomula (II) wherein R^5 is C_{1-4}alkyl, phenyl or phenyl substituted with one or two halo, C_{1-4}alkyl or C_{1-4}alkyloxy substituents; and R^6 is hydrogen or C_{1-4}alkyl.

More preferred compounds are those preferred compounds of formula (I) wherein R^1 is phenyl or halophenyl, and R^2 and R^3 are both independently hydrogen or C_{1-4}alkyl.

Other more preferred compound are those preferred compounds of formula (II) wherein R^5 is phenyl or halophenyl and R^6 is hydrogen or C_{1-4}alkyl.

Most preferred compounds are 5-[(1H-imidazol-1-yl)phenylmethyl]-1H-benzimidazole, (±)-5-[(1H-imidazol-1-yl)phenylmethyl]-2-methyl-1H-benzimidazole, 5-[(1H-imidazol-1-yl)phenylmethyl]-1-methyl-1H-benzimidazole, 5-[1-(1H-imidazole-1-yl)-2-methylpropyl]-2-methyl-1H-benzimidazole, 5-[(3-chlorophenyl) (1H-imidazol-1-yl)methyl]-1H-benzimidazole or (±)-5-[(1H-imidazol-1-yl)phenylmethyl]-2-methyl-1H-benzimidazole, the pharmaceutically acceptable acid addition salts and possible stereoisomers thereof.

From formulae (I) and (II) it is evident that the compounds of this invention may have several asymmetric carbon atoms in their structure. Each of these chiral centers may be present in a R- and a S-configuration, this R- and S-notation being in correspondence with the rules described by R.S. Cahn, C. Ingold and V. Prelog in Angew. Chem., Int. Ed. Engl., 5, 385, 511 (1966).

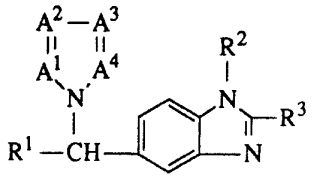
Pure stereochemically isomeric forms of the compounds of formulae (I) and (II) may be obtained by the application of art-known procedures. Diastereoisomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g., counter current distribution, and enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids.

Pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically.

Stereochemically isomeric forms of the compounds of formulae (I) and (II) are naturally intended to be embraced within the scope of the invention.

Some of the compounds of formula (I) and (II) which can be used as active ingredient in the compositions and methods of treatment according to the present invention are listed in the following tables with the purpose of illustrating the invention and not to limit it thereto.

Table 1

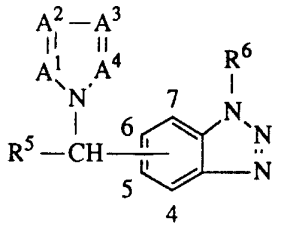


Comp No.	p*	-A^1=A^2-A^3=A^4-	R^1	R^2	R^3	mp.(°C)/ salt
1	5	-CH=CH-N=CH-	C_6H_5-	H-	H-	186.2
2	5	-CH=CH-N=CH-	C_6H_5-	H-	CH_3-	118.4
3	5	-CH=CH-N=CH-	2-thienyl-	H-	H-	101.0
4	5	-CH=CH-N=CH-	2-thienyl-	H-	CH_3-	108.9
5	5	-CH=CH-N=CH-	4-F-C_6H_4-	H-	CH_3-	110.6
6	5	-CH=CH-N=CH-	2,4-$(Cl)_2$-C_6H_3-	H-	CH_3-	138.4
7	5	-CH=CH-N=CH-	3-Cl-C_6H_4-	H-	CH_3-	113.3
8	5	-CH=CH-N=CH-	3-CH_3-C_6H_4-	H-	H-	104.8

Comp No.	p*	-A^1=A^2-A^3=A^4-	R^1	R^2	R^3	mp.(°C)/ salt
9	5	-CH=CH-N=CH-	C_6H_5-	H-	2-pyridyl-	123.3
10	5	-CH=CH-N=CH-	c.C_3H_5-	H-	H-	73.5
11	5	-CH=CH-N=CH-	C_6H_5-	H-	3-pyridiyl-	133.1
12	6	-N=CH-N=CH-	H-	OH-	3-pyridiyl-	219.3
13	5	-CH=CH-N=CH-	C_6H_5-	H-	C_6H_5-	134.5
14	6	-N=CH-N=CH-	H-	OCH_3-	3-pyridiyl-	141.5
15	5	-N=CH-N=CH-	H-	H-	CH_3-	241.0/ 2HCl
16	5	-N=CH-N=CH-	H-	H-	H-	184.4
17	5	-N=CH-N=CH-	H-	H-	C_6H_5-	239.7
18	5	-N=CH-N=CH-	H-	H-	3-pyridiyl-	222.5
19	5	-CH=CH-N=CH-	C_6H_5-	H-	C_6H_5-CH_2-	189.9
20	5	-CH=CH-N=CH-	C_4H_9-	H-	CH_3-	-
21	5	-CH=CH-N=CH-	C_6H_5-	CH_3-	H-	138.7
22	5	-CH=CH-N=CH-	i-C_3H_7-	H-	CH_3-	214.8/2HCl/H_2O
23	5	-CH=CH-N=CH-	C_6H_5-	H-	—CH=CH— 	134.7 (E)
24	5	-CH=CH-N=CH-	C_3H_7-	H-	CH_3-	174.2/1.5$(COOH)_2$
25	5	-CH=CH-N=CH-	C_6H_5-	H-	—CH=CH— 	140.6 (E)
26	5	-CH=CH-N=CH-	2-furanyl-	H-	H-	150.9
27	5	-CH=CH-N=CH-	C_6H_5-	H-	CH_3-	77.2/H_2O/**
28	5	-CH=CH-N=CH-	3-Cl-C_6H_4-	H-	H-	200.2/HCl
29	5	-CH=CH-N=CH-	3-Cl-C_6H_4-	CH_3-	H-	131.2/1/2H_2O
30	5	-CH=CH-N=CH-	3-Cl-C_6H_4-	C_6H_5-CH_2-	H-	59.6/1/2EtOH
31	5	-N=CH-N=CH-	3-Cl-C_6H_4-	H-	CH_3-	205.4/2$(COOH)_2$
32	5	-N=CH-N=CH-	3-Cl-C_6H_4-	H-	H-	210.0
33	5	-CH=CH-N=CH-	C_6H_5-	H-	CH_3-	128.5 / H_2O

* : p indicates the position of the 1H-azol-1-ylmethylmoiety on the benzimidazole ring
** = $[\alpha]_D$= -29.57° (c = 0.5% in methanol)

Table 2



4

Comp. No.	-A^1=A^2-A^3=A^4-	p*	R^5	R^6	mp.(°C)/ salt
34	-CH=CH-N=CH-	5	C_6H_5-	CH_3-	111.9/HNO_3
35	-CH=CH-N=CH-	5	C_6H_5-	H-	178.8
36	-CH=CH-N=CH-	6	C_6H_5-	CH_3-	102.7
37	-N=CH-N=CH-	5	C_6H_5-	H-	182.7
38	-CH=CH-N=CH-	6	4-Cl-C_6H_4-	CH_3-	151.5/ HCl/H_2O
39	-N=CH-N=CH-	6	4-Cl-C_6H_4-	CH_3-	178.9

*p indicates the position of the 1-H-azol-1-ylmethyl moiety on the benzotriazole ring.

The use of the compounds of formula (I) and (II), their pharmaceutically acceptable acid addition salts and their possible stereochemically isomeric forms for the manufacture of a medicament for treating mammals suffering from disorders which are characterized by an increased proliferation and/or abnormal differentiation of epithelial cells the growth of which is sensitive to the action of retinoids, is based on their useful property to delay the metabolism of retinoids, such as, all-*trans*-retinoic acid, 13-*cis*-retinoic acid and their derivatives. The latter results in more sustained / higher tissue concentrations of retinoids and improved control of differentiation and growth of various cell types. Said property to delay the metabolism of retinoids can easily be evidenced in various in *vivo* experiments. A particular test procedure is described hereinafter as the "Metabolism of endogenous or exogenously administered all-*trans*-retinoic acid"-test . As such, the compounds of formula (I) and (II) can be used to control the rate of growth and differentiation of normal, preneoplastic and neoplastic epithelial cells. The ability of retinoids, such as, 13-*cis*-retinoic acid, all-*trans*-retinoic acid and their derivatives to modulate differentiation and proliferation in several cell types is extensively studied and reviewed in J. Clin. Chem. Clin, Biochem., 26, 479-488 (1983); Pharmacological Reviews 36, 935-1005, (1984), Arch. Dermatol. 117, 160-180; (1981) and Journal of Medicinal Chemistry 25, 1269-1277, (1982).

The compounds of formulae (I) and (II), their pharmaceutically acceptable acid addition salts and their possible stereochemically isomeric forms are therefore useful to treat disorders which are characterized by an increased proliferation and/or abnormal differentiation of epithelial cells. In particular the compounds of the invention can be used for treatment of carcinoma, which is essentially a derailment of cellular

differentiation occurring in epithelial tissues. The compounds of the invention do not only exhibit an anticarcinogenic effect on estrogen or androgen dependent carcinoma cells but also show an unexpected effect on cells of which the growth and differentiation is not substantially mediated by or insensitive to the actions of androgens or estrogens, in particular on cells of which the growth and differentiation is sensitive to the actions of retinoids. Other uses include the ability to cure and/or reduce a variety of disorders of keratinization such as, for example, acne, psoriasis, lamellar ichthyosis, plantar warts, callosites, acanthosis nigricans, lechen planus, molluscum, melasma, corneal epithelial abrasion, geograpic tongue, Fox-Fordyce disease, cutaneous metastatic melanoma and heloids, epidermolytic hyperkeratosis, Darier's disease, pityriasis rubra pilaris, congenital ichthyosiform erythroderma, hyperkeratosis palmaris et plantaris, and similar disordes.

The anti-tumor activity, especially in retinoic acid sensitive tumors, may be demonstrated in several retinoic acid-sensitive cell lines and solid tumors such as, for example, in Ta3-Ha induced mamma tumors in female mice.

Those of skill in treating disorders which are characterized by an excessive proliferation and/or abnormal differentiation of tissues could determine the effective amount from the test results presented hereinafter. In general it is contemplated than an effective amount would be from 0.001 mg/kg to 50 mg/kg body weight and more preferably from 0.01 mg/kg to 10 mg/kg body weight.

The compounds of formulae (I) and (II) are most preferably applied in the form of appropriate compositions. As appropriate compositions there may be cited all compositions usually employed for systemically or topically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in acid-addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and

tablets. Because of their ease in administration, tablets and capsules represents the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositons suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin.

As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs, e.g., creams, gellies, dressings, shampoos, tinctures, pastes, ointments, salves, powders, liquid or semi-liquid formulation and the like. Application of said compositions may be by aerosol e.g. with a propellent such as nitrogen carbon dioxide, a freon, or without a propellent such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab. In particular compositions, semisold compositions such as salves, creams, pastes, gellies, ointments and the like will conveniently be used.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discreate units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powders packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Other such compositions are preparations of the cosmetic type, such as toilet waters, packs, lotions, skin milks or milky lotions. Said preparations contain, besides the active ingredient of formula (I) or (II), components usually employed in such preparations. Examples of such components are oils, fats, waxes, surfactants, humectants, thickening agents, antioxidants, viscosity stabilizers, chelating agents, buffers, preservatives, per-

fumes, dyestuffs, lower alkanols, and the like. If desired, further ingredients may be incorporated in the compositions, e.g. antiinflammatory agents, antibacterials, antifungals, disinfectants, vitamins, sunscreens, antibiotics, or other anti-acne agents.

Examples of oils comprise fats and oils such as olive oil and hydrogenated oils; waxes such as beeswax and lanolin; hydrocarbons such as liquid paraffin, ceresin, and squalane; fatty acids such as stearic acid and oleic acid; alcohols such as cetyl alcohol, stearyl alcohol, lanolin alcohol, and hexadecanol; and esters such as isopropyl myristate, isopropyl palmitate and butyl stearate. As examples of surfactants there may be cited anionic surfactants such as sodium stearate, sodium cetylsulfate, polyoxyethylene laurylether phosphate, sodium N-acyl glutamate; cationic surfactants such as stearyldimethylbenzylammonium chloride and stearyltrimethylammonium chloride; ampholytic surfactants such as alkylaminoethylglycine hydrochloride solutions and lecithin; and nonionic surfactants such as glycerin monostearate, sorbitan monostearate, sucrose fatty acid esters, propylene glycol monostearate, polyoxyethylene oleylether, polyethylene glycol monostearate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene coconut fatty acid monoethanolamide, polyoxyethylene polyoxypropylene glycol (e.g. the materials sold under the trademark "Pluronic"), polyoxyethylene castor oil, and polyoxyethylene lanolin. Examples of humectants include glycerin, 1,3-butylene glycol, and propylene glycol; examples of lower alcohols include ethanol and isopropanol; examples of thickening agents include xanthan gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyethylene glycol and sodium carboxymethyl cellulose; examples of antioxidants comprise butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, citric acid and ethoxyquin; examples of chelating agents include disodium edetate and ethanehydroxy diphosphate; examples of buffers comprise citric acid, sodium citrate, boric acid, borax, and disodium hydrogen phosphate; and examples of preservatives are methyl parahydroxybenzoate, ethyl parahydroxybenzoate, dehydroacetic acid, salicylic acid and benzoic acid.

For preparing ointments, creams, toilet waters, skin milks, and the like, typically from 0.01 to 10% in particular from 0.1 to 5% and more in particular from 0.2 to 2.5% of the active ingredient of formula (I) or (II) will be incorporated in said compositions. In ointments or creams, the carrier for example consists of 1 to 20%, in particular 5 to 15% of a humectant, 0.1 to 10% in particular from 0.5 to 5% of a thickener and water; or said carrier may consist of 70 to 99%, in particular 20 to 95% of a surfactant, and 0 to 20%, in particular 2.5 to 15% of a fat; or 80 to 99.9% in particular 90 to 99% of a thickener; or 5 to 15% of a surfactant, 2-15% of a humectant, 0 to 80% of an oil, very small (<2%) amounts of preservative, colouring agent and/or perfume, and water. In a toilet water,

the carrier for example consists of 2 to 10% of a lower alcohol, 0.1 to 10% or in particular 0.5 to 1% of a surfactant, 1 to 20%, in particular 3 to 7% of a humectant, 0 to 5% of a buffer, water and small amounts (<2%) of preservative, dyestuff and/or perfume. In a skin milk, the carrier typically consists of 10-50% of oil, 1 to 10% of surfactant, 50-80% of water and 0 to 3% of preservative and/or perfume. In the aforementioned preparations, all % symbols refer to weight by weight percentage. The humectant, surfactant, oil, etc... referred to in said preparations may be any such component used in the cosmetic arts but preferably will be one or more of the components mentioned hereinabove. Further, when in the above compositions one or more of the components make up the major part of the composition, the other ingredients can evidently be not present at their indicated maximum concentration and therefore will make up the remainder of the composition.

Particular compositions for use in the method of the present invention are those wherein the active ingredient of formula (I) or (II) is formulated in liposome-containing compositions. Liposomes are artificial vesicles formed by amphiphatic molecules such as polar lipids, for example, phosphatidyl cholines, ethanolamines and serines, sphingomyelins, cardiolipins, plasmalogens, phosphatidic acids and cerebiosides. Liposomes are formed when suitable amphiphathic molecules are allowed to swell in water or aqueous solutions to form liquid crystals usually of multilayer structure comprised of many bilayers separated from each other by aqueous material (also referred to as coarse liposomes). Another type of liposome known to be consisting of a single bilayer encapsulating aqueous material is referred to as a unilamellar vesicle. If water-soluble materials are included in the aqueous phase during the swelling of the lipids they become entrapped in the aqueous layer between the lipid bilayers.

Water-soluble active ingredients such as, for example, most of the salt forms of the compound of formula (I) or (II) are encapsulated in the aqueous spaces between the molecular layers. The lipid soluble active ingredient of formula (I) or (II) is predominantly incorporated into the lipid layers, although polar head groups may protrude from the layer into the aqueous space. The encapsulation of these compounds can be achieved by a number of methods. The method most commonly used involves casting a thin film of phospholipid onto the walls of a flask by evaporation from an organic solvent. When this film is dispersed in a suitable aqueous medium, multilamellar liposomes are formed. Upon suitable sonication, the coarse liposomes form smaller similarly closed vesicles.

Water-soluble active ingredients are usually incorporated by dispersing the cast film with an aqueous solution of the compound. The unencapsulated compound is then removed by centrifugation, chromatography, dialysis or other art-known suitable procedures. The lipid-soluble active ingredient is usually incorporated by dissolving it in the organic solvent with the phospholipid prior to casting the film. If the solubility of the material in the lipid phase is not exceeded or the amount present is not in excess of that which can be bound to the lipid, liposomes prepared by the above method usually contain most of the material bound in the lipid bilayers; separation of the liposomes from unencapsulated material is not required.

A particularly convenient method for preparing liposome formulated forms of the active ingredient of formula (I) or (II) is the method described in EP-A-253,619, incorporated herein by reference. In this method, single bilayered liposomes containing encapsulated active ingredients are prepared by dissolving the lipid component in an organic medium, injecting the organic solution of the lipid component under pressure into an aqueous component while simultaneously mixing the organic and aqueous components with a high speed homogenizer or mixing means, whereupon the liposomes are formed spontaneously.

The single bilayered liposomes containing the encapsulated active ingredient of formula (I) or (II) can be employed directly or they can be employed in a suitable pharmaceutically acceptable carrier for topical administration. The viscosity of the liposomes can be increased by the addition of one or more suitable thickening agents such as, for example xanthan gum, hydroxypropyl cellulose, hydroxypropyl methylcellulose and mixtures thereof. The aqueous component may consist of water alone or it may contain electrolytes, buffered systems and other ingredients, such as, for example, preservatives. Suitable electrolytes which can be employed include metal salts such as alkali metal and alkaline earth metal salts. The preferred metal salts are calcium chloride, sodium chloride and potassium chloride. The concentration of the electrolyte may vary from zero to 260 mM, preferably from 5 mM to 160 mM. The aqueous component is placed in a suitable vessel which can be adapted to effect homogenization by effecting great turbulence during the injection of the organic component. Homogenization of the two components can be accomplished within the vessel, or, alternatively, the aqueous and organic components may be injected separately into a mixing means which is located outside the vessel. In the latter case, the liposomes are formed in the mixing means and then transferred to another vessel for collection purpose.

The organic component consists of a suitable non-toxic, pharmaceutically acceptable solvent such as, for example ethanol, glycerol, propylene glycol and polyethylene glycol, and a suitable phospholipid which is soluble in the solvent. Suitable phospholipids which can be employed include lecithin, phosphatidylcholine, phosphatidylethanol-amine, phosphatydylserine, phosphatidylinositol, lysophosphatidylcholine and phospha-tidyl glycerol, for example. Other lipophilic additives may be employed in order to selectively modify the characteristics of the liposomes. Examples of such other additives include stearylamine, phosphatidic acid, tocopherol, cholesterol and lanolin extracts.

It may be advantageous to use micronized forms of the active ingredient of formula (I) or (II), i.e., material having an average particle size of less than 10 microns, as the high surface area will facilitate the dissolution of the liposomal components.

In addition, other ingredients which can prevent oxidation of the phospholipids may be added to the organic component. Examples of such other ingredients include tocopherol, butylated hydroxyanisole, butylated hydroxytoluene, ascorbyl palmitate and ascorbyl oleate. Preservatives such as benzoic acid, methyl paraben and propyl paraben may also be added.

The liposome-formulated forms of the active ingredient of formula (I) or (II), particularly those obtained in the above-referred method of preparing such liposome formulated forms, may be used as such or in combination with any of the afore-mentioned carriers to prepare ointments, creams, gelées, toilet waters, etc...

Apart from the above-described compositions, use may be made of covers, e.g. plasters, bandages, dressings, gauze pads and the like, containing an appropriate amount of a composition as referred hereinabove. In some cases use may be made of plasters, bandages, dressings, gauze pads and the like which have been impregnated or sprinkled with a liquid formulation containing the active agent, e.g. with an aseptic aqueous solution, or strewn with a powdery solid composition, or smeared, covered or coated with a semi-liquid composition.

It can be demonstrated that the retinoic acids and the compounds of formula (I) or (II) act in a synergistic manner. Indeed, the combined effect of both substances is greater than the sum of their respective effects when administered separately. As evidenced by the data obtained in the "vaginal keratinization"-test described hereinafter. The above described retinoic acid containing compositions are particularly useful for treating acne or for retarding the effects of aging of the skin and generally improve the quality of the skin, particularly human facial skin. A pharmaceutical or cosmetical composition containing retinoic acid or a derivative thereof as the active ingredient in intimate

admixture with a dermatologically acceptable carrier can be prepared according to conventional compounding techniques, such as those known for topical application of retinoic acid and its derivatives. Conventional pharmaceutical compounding techniques for topical application of retinoic acid are described for example in, U.S. Pat. Nos. 3,906,108 and 4,247,547, which are incorporated herein by reference. Preferred composition for topical application are in form of a cream, ointment or lotion comprising from 0.005 to 0.5% (particularly from 0.01 to 0.1%) all-*trans*-retinoic acid, 13-*cis*-retinoic acid or a derivative thereof and from 0.1 to 5% of a compound of formula (I) and/or (II), a dermatologically acceptable acid addition salt thereof or a stereochemically isomeric form thereof, in a semi-solid or liquid diluent or carrier.

These preferred composition should preferably be non-irritating and as far as possible they should be odorless and non-toxic. For convenience in applying to the skin, the composition usually contain, besides water or an organic solvent, several of certain organic emollients, emulsifiers for the aqueous and/or non aqueous phases of the compositions, wetting agents preservatives and agents that facilitate the penetration and remainence of the active agents in the skin.

In use, the retinoic acid containing compositions of the invention are applied topically to the area to be treated or protected, at regular intervals, as needed, generally about 7 to about 21 times per week. The duration of the treatment will depend upon the nature and severity of the condition to be treated as well as the frequency of application of the composition.

The following examples are intended to illustrate the scope of the present invention in all its aspects, and not to limit it thereto.

Experimental part

A. Pharmaceutical Examples

Example 1

Metabolism of exogenously administered all-*trans*-retinoic acid

Male Wistar rats weighing 200~210 g were orally treated with vehicle (PEG 200) or with 40 mg/kg of a compound of formula (I). One hour later, the animals were anesthetized with ether and injected intrajugularly with 0.50 ml saline solution containing 20 µg of all-*trans*-retinoic acid. Two hours after this injection, rats were killed by decapitation and blood was collected on heparin. Blood samples were centrifuged (1000 g, 15 min) and plasma was recovered to determine the quantity of plasmatic all-*trans*-retinoic acid. The samples were analyzed by means of HPLC with UV-detection at 350 nm. Quatification was achieved by peak area integration and external standardization.

Under the conditions used, plasma concentrations of the retinoic acid in vehicle-pretreated animals were not detectable (<0.5 ng/ml), whereas compound nos. 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 13, 19, 20, 21, 22, 24, 28, 29, 30, 33 and 34 enhanced the recovery of all-*trans*-retinoic acid from the plasma to a least 8 ng/ml after dosing with 40 mg/kg.

Example 2

Metabolism of endogenous all-*trans*-retinoic acid

Male Wistar rats weighing 200~210 g were orally treated with vehicle (PEG 200) or with 40 mg/kg of a compound of formula (I). Two hours after drug administration, the rats were killed by decapitation and blood was collected on heparin. Blood samples were centrifuged (1000 g, 15 min) and plasma was recovered to determine the quantity of plasmatic all-*trans*-retinoic acid. The samples were analyzed by means of HPLC with UV-detection at 350 nm. Quatification was achieved by peak area integration and external standardization. Under the conditions used, plasma concentrations of the retinoic acid in vehicle-pretreated animals were not detectable (<0.5 ng/ml), whereas compound nos. 1, 2, 7, 13, 21, 22, 27, 28 and 33 enhanced the recovery of all-*trans*-retinoic acid from the plasma to a least 1 ng/ml.

Example 3

Vaginal keratinization.

Ovariectomized rats were injected subcutaneously with a sesame oil solution containing 100 µg of estradiol undecylate (Progynon Dépôt®, Schering) in a volume of 0.1 ml per 100 g body weight. One and two days later, the animals were treated intravaginally with 200 µl of vehicle (PEG 200), all-*trans*-retinoic acid (1 or 4 µg) or all-*trans*-retinoic acid (1 µg) together with 3 mg of a compound of formula (I). One day after the second topical treatment, the animals were sacrificed. Vaginas were immediately dissected and trimmed of fat and connective tissue. The third middle of the organ (0.5 cm length) was fixed in liquid nitrogen for histological analysis. Hereto, a series of 10 µm cross-section were cut at -25°C, mounted onto gelatin-coated glass slides and stained with hematoxylin and eosin. The slides were examined under light microscopy at 100-400 x magnification. The condition of the vaginal mucosa was scored (keratinization score) as

0 : absence of keratinized squamae attached to the epithelial cells.

\+ : presence of keratinized squamae partially covering the epithelial cells.

++ : presence of keratinized squamae covering the entire vaginal epithellium.

Results

	score
vehicle (PEG 200)	++
4 µg retinoic acid	0
1 µg retinoic acid	++
1µg retinoic acid + 3 mg comp. No.21	0

C) Composition Examples

The following formulations exemplify typical pharmaceutical and cosmetical compositions in dosage unit form suitable for systemic or topical administration to warm-blooded animals in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

Example 4 : ORAL DROPS

500 g of the A.I. was dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol at 60≈80°C. After cooling to 30≈40°C there were added 35 l of polyethylene glycol and the mixture was stirred well. Then there was added a solution of 1750 g of sodium saccharin in 2.5 l of purified water and while stirring there were added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg of the A.I. (per ml). The resulting solution was filled into suitable containers.

Example 5 : ORAL SOLUTION

9 g of methyl 4-hydroxybenzoate and 1 part of propyl 4-hydroxy-benzoate were dissolved in 4 l of boiling purified water. In 3 l of this solution were dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the A.I. The latter solution was combined with the remaining part of the former solution and 12 l 1,2,3-propane-triol and 3 l of sorbitol 70% solution were added thereto. 40 g of sodium saccharin were dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the A.I. per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

Example 6 : CAPSULES

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of the A.I.

Example 7 : FILM-COATED TABLETS

Preparation of tablet core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch was mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone (Kollidon-K 90®) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 g microcrystalline cellulose (Avicel®) and 15 g hydrogenated vegetable oil (Sterotex ®). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of 10 g methyl cellulose (Methocel 60 HG®) in 75 ml of denaturated ethanol there was added a solution of 5 g of ethyl cellulose (Ethocel 22 cps ®) in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propane-triol. 10 g of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension (Opaspray K-1-2109®) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example 8 : INJECTABLE SOLUTION

1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I..The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg A.I. per ml. The solution was sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

Example 9 : SUPPOSITORIES

3 g A.I. was dissolved in a solution of 3 g 2,3-dihydroxybutane-dioic acid in 25 ml polyethylene glycol 400. 12 g surfactant (SPAN(®) and triglycerides (Witepsol 555®)

q.s. ad 300 g were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37-38°C to form 100 suppositories each containing 30 mg of the active ingredient.

Example 10 : 2% CREAM

75 mg of stearyl alcohol, 2 mg of cetyl alcohol, 20 mg of sorbitan monostearate and 10 mg of isopropyl myristate are introduced into a doublewall jacketed vessel and heated until the mixture has completely molten. This mixture is added to a separately prepared mixture of purified water, 200 mg of propylene glycol and 15 mg of polysorbate 60 having a temperature of 70 to 75°C while using a homogenizer for liquids. The resulting emulsion is allowed to cool to below 25°C while continuously mixing. A solution of 20 mg of active ingrediënt of formula (I) or (II), 1 mg of polysorbate 80 and purified water and a solution of 2 mg of sodium sulfite anhydrous in purified water are next added to the emulsion while continuously mixing. The cream (1 g) is homogenized and filled into suitable tubes.

Example 11 : 2% TOPICAL GEL

To a solution of 200 mg of hydroxypropyl β-cyclodextrine in purified water is added 20 mg of active ingrediënt of formula (I) or (II) while stirring. Hydrochloric acid is added until complete solution and then sodium hydroxide is added until pH 6.0. This solution is added to a dispersion of 10 mg of carrageenan PJ in 50 mg of propylene glycol while mixing. While mixing slowly the mixture is heated to 50°C and allowed to cool to about 35°C whereupon 50 mg of ethyl alcohol 95% is added. The rest of the purified water is added q.s. ad 1 g and the mixture is mixed to homogenous.

Example 12 : 2% TOPICAL CREAM

To a solution of 200 mg of hydroxypropyl β-cyclodextrine in purified water is added 20 mg of active ingrediënt of formula (I) or (II) while stirring. Hydrochloric acid is added until complete solution and next sodium hydroxide is added until pH 6.0. While stirring, 50 mg of glycerol and 35 mg of polysorbate 60 are added and the mixture is heated to 70°C. The resulting mixture is added to a mixture of 100 mg of mineral oil, 20 mg of stearyl alcohol, 20 mg of cetyl alcohol, 20 mg of glycerol monostearate and 15 mg of sorbate 60 having a temperature of 70°C while mixing slowly. After cooling down to below 25°C, the rest of the purified water is added q.s. ad 1 g and the mixture is mixed to homogenous.

Example 13 : 2% LIPOSOME FORMULATION

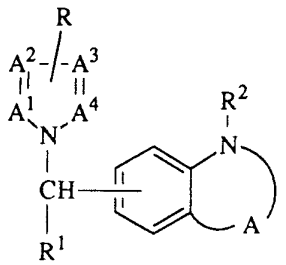
A mixture of 2 g of active ingrediënt of formula (I) or (II) microfine, 20 g of phosphatidyl choline, 5 g of cholesterol and 10 g of ethyl alcohol is stirred and heated at 55-60°C until complete solution and is added to a solution of 0.2 g of methyl paraben, 0.02 g of propyl paraben, 0.15 g of disodium edetate and 0.3 g of sodium chloride in purified water while homogenizing. 1.5 g of hydroxypropylmethylcellulose in purified water is added ad 100 g and the mixing is continued until swelling is complete.

Example 14 : 2% LIPOSOME FORMULATION

A mixture of 10 g of phosphatidyl choline and 1 g of cholesterol in 7.5 g of ethyl alcohol is stirred and heated at 40°C until complete solution. 2 g of active ingrediënt of formula (I) or (II) microfine is dissolved in purified water by mixing while heating at 40°C. The alcoholic solution is added slowly to the aqueous solution while homogenizing during 10 minutes. 1.5 g of hydroxypropylmethylcellulose in purified water is added while mixing until swelling is complete. The resulting solution is adjusted to pH 5.0 with sodium hydroxide 1 N and diluted with the rest of the purified water ad 100 g.

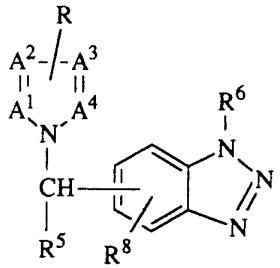
Claims

1. A pharmaceutical or cosmetical composition comprising an inert carrier, an effective amount of a retinoic acid or a derivative thereof, or a stereochemically isomeric form thereof and an effective amount of a compound of formula



(I)

or



(II)

an acid addition salt thereof or a stereochemically isomeric form thereof, wherein R, R^1, R^2, $-A^1=A^2-A^3=A^4-$ and A in formula (I) have the following meaning

$-A^1=A^2-A^3=A^4-$ is a bivalent radical having the formula

-CH=N-CH=CH- (x);

-CH=N-CH=N- (y); or

-CH=N-N=CH- (z);

R is hydrogen or C_{1-6}alkyl;

R^1 is hydrogen; C_{1-10}alkyl; C_{3-7}cycloalkyl; Ar^1 or Ar^1-C_{1-6}alkyl;

R^2 is hydrogen; C_{3-7}cycloalkyl; Ar^1; C_{1-10}alkyl; C_{1-6}alkyl substituted with Ar^1 or C_{3-7}cycloalkyl; hydroxy; C_{1-10}alkyloxy; C_{1-6}alkyloxy substituted with Ar^1 or C_{3-7}cycloalkyl; C_{3-6}alkenyloxy optionally substituted with Ar^2; C_{3-6}alkynyloxy optionally substituted with Ar^2; or Ar^1-oxy;

A is a bivalent radical having the formula

$-CR^3=N-$ (a) or



(b),

wherein the carbon atom in the bivalent radical (a) and (b) is connected to $-NR^2$;

said R^3 being hydrogen; halo; C_{1-4}alkyl substituted with up to 4 halo atoms; C_{3-7}cycloalkyl; Ar^1; quinolinyl; indolinyl; C_{1-10}alkyl; C_{1-6}alkyl substituted with Ar^1, C_{3-7}cycloalkyl, quinolinyl, indolinyl or hydroxy; C_{1-10}alkyloxy; C_{1-6}alkyloxy substituted with Ar^1 or C_{3-7}cycloalkyl; C_{2-6}alkenyl optionally substituted with Ar^1; Ar^2-oxy; C_{1-6}alkyloxycarbonyl; carboxyl; C_{1-6}alkylcarbonyl; Ar^1-carbonyl or Ar^1-(CHOH)-;

said X being O or S;
said R^4 being hydrogen, C_{1-6}alkyl or Ar^2-C_{1-6}alkyl;
wherein Ar^1 is phenyl, substituted phenyl, pyridinyl, aminopyridinyl, imidazolyl, thienyl, halothienyl, furanyl, halofuranyl or thiazolyl; and Ar^2 is phenyl or substituted phenyl; said substituted phenyl in Ar^1 and Ar^2 being phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, amino, mono- and di(C_{1-6}alkyl)amino, nitro, carboxyl, formyl and C_{1-6}alkyloxycarbonyl; and wherein

R, R^5, R^6, R^7 and -A^1=A^2-A^3=A^4- in formula (II) have the following meaning
-A^1=A^2-A^3=A^4- is a bivalent radical having the formula
-CH=N-CH=CH- (x);
-CH=N-CH=N- (y); or
-CH=N-N=CH- (z);
R is hydrogen or C_{1-6}alkyl;
R^5 is hydrogen; C_{1-10}alkyl; C_{3-7}cycloalkyl; Ar^3; Ar^4-C_{1-6}alkyl; C_{2-6}alkenyl or C_{2-6}alkynyl;
R^6 is hydrogen; C_{1-10}alkyl optionally substituted with Ar^3, C_{3-7}cycloalkyl, hydroxy or C_{1-6}alkyloxy; Ar^3; C_{2-6}alkenyl; C_{2-6}alkynyl; C_{3-7}cycloalkyl; bicyclo-[2.2.1]heptan-2-yl; 2,3-dihydro-1H-indenyl; 1,2,3,4-tetrahydronaphthalenyl; or a radical of formula OR^7,
R^7 is hydrogen; C_{2-6}alkenyl optionally substituted with Ar^4; C_{2-6}alkynyl; pyrimidinyl, di(Ar^4)methyl; 1-C_{1-4}alkyl-4-piperidinyl; or C_{1-10}alkyl optionally substituted with halo, hydroxy, C_{1-6}alkyloxy, amino, mono- and di(C_{1-6}alkyl)-amino, trifluoromethyl, carboxyl, C_{1-6}alkyloxycarbonyl, Ar^3, Ar^4-O-, Ar^4-S-, C_{3-7}cycloalkyl, 2,3-dihydro-1,4-benzodioxinyl, 1H-benzimidazolyl, C_{1-4}alkyl substituted 1H-benzimidazolyl, (1,1'-biphenyl)-4-yl or with 2,3-dihydro-2-oxo-1H-benzimidazolyl;
R^8 is hydrogen, nitro, amino, mono- and di(C_{1-6}alkyl)amino, halo, C_{1-6}alkyl, hydroxy or C_{1-6}alkyloxy;
wherein Ar^3 is phenyl, substituted phenyl, naphthalenyl, pyridinyl, aminopyridinyl, imidazolyl, triazolyl, thienyl, halothienyl, furanyl, C_{1-6}alkylfuranyl, halofuranyl or thiazolyl; Ar^4 is phenyl, substituted phenyl or pyridinyl, said substituted phenyl in Ar^3 and Ar^4 being phenyl substituted with up to 3 substituents each independently selected from halo, hydroxy, hydroxymethyl, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyl-oxy, C_{1-6}alkyloxycarbonyl, carboxyl, formyl, (hydroxyimino)methyl, cyano, amino, mono- and di(C_{1-6}alkyl)amino and nitro.

2. A pharmaceutical composition according to claim 1 which comprises a pharmaceutically acceptable carrier, a therapeutically effective amount of a compound of formula (I), a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof and a therapeutically effective amount of a retinoic acid, a derivative thereof or a stereochemically isomeric form thereof.

3. A composition according to claim 2 wherein the 1H-azol-1-ylmethyl moiety in the compound of formula (I) is substituted on either the 5 or 6 position of the benzimidazole ring; R is hydrogen; R^1 is hydrogen; C_{1-6}alkyl; C_{3-7}cycloalkyl; phenyl; substituted phenyl; thienyl or furanyl optionally substituted with halo; R^2 is hydrogen; C_{3-7}cycloalkyl; phenyl; substituted phenyl; pyridinyl; C_{1-6}alkyl optionally monosubstituted with phenyl, C_{3-7}cycloalkyl, pyridinyl or thienyl; hydroxyl, C_{1-6}alkyloxy optionally monosubstituted with phenyl, pyridinyl, thienyl or C_{3-6}cycloalkyl; C_{3-6}alkenyloxy optionally monosubstituted with phenyl; or C_{3-6}alkynyloxy; R^3 is hydrogen; C_{1-4}alkyl substituted with up to 4 halo atoms; C_{3-7}cycloalkyl; phenyl; substituted phenyl; imidazolyl; thiazolyl; thienyl; furanyl; quinolinyl; pyridinyl optionally substituted with amino, C_{1-10}alkyl; C_{1-5}alkyl optionally monosubstituted with phenyl, pyridinyl, imidazolyl, thienyl, indolyl or hydroxyl; C_{1-4}alkyloxy optionally monosubstituted with phenyl; C_{2-6}alkenyl optionally monosubstituted with pyridinyl, furanyl, imidazolyl or phenyl; carboxyl; C_{1-4}alkyloxycarbonyl; phenylcarbonyl; or hydroxy and phenylmethyl; and R^4 is hydrogen or phenylC_{1-4}alkyl.

4. A composition according to claim 3 wherein R^1 is C_{1-4}alkyl, phenyl, phenyl substituted with one or two halo; C_{1-4}alkyl or C_{1-4}alkyloxy substituents, or thienyl; and R^2 is hydrogen or C_{1-4}alkyl; R^3 is hydrogen or C_{1-4}alkyl.

5. A composition according to any of claims 1 to 4 wherein the retinoic acid is *trans*-retinoic acid or 13-*cis*-retinoic acid.

6. A process of preparing a composition as claimed in any of claims 1 to 5, characterized in that the active ingredients are intimately mixed with the carrier.

7. A pharmaceutical composition according to claim 1 which comprises a pharmaceutically acceptable carrier, a therapeutically effective amount of a compound of formula (II), a pharmaceutically acceptable acid addition salt or a stereochemically

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isomeric form thereof and a therapeutically effective amount of a retinoic acid, a derivative thereof or a stereochemically isomeric form thereof.

8. The use of a composition as claimed in claim 7 for the manufacture of a medicament for topically treating acne.

9. The use of a compound of formula (II) as defined in claim 1, a pharmaceutically acceptable acid addition salt thereof or a stereochemically isomeric form thereof, for the manufacture of a medicament for treating subjects suffering from disorders which are characterized by an increased proliferation and/or abnormal differentation of normal, preneoplastic or neoplastic epithelial cells the growth of which is sensitive to the action of retinoids.

10. Use according to claim 9 wherein the 1H-azol-1-ylmethyl moiety in the compound of formula (II) is substituted on either the 5 or 6 position of the benzotriazole ring; R is hydrogen; R^5 is hydrogen; C_{1-6}alkyl; phenyl; substituted phenyl; C_{3-7}cycloalkyl; thienyl or furanyl optionally substited with halo; R^6 is hydrogen; C_{1-6}alkyl; C_{3-6}alkenyl; C_{3-6}alkynyl; C_{3-7}cycloalkyl; phenyl; substituted phenyl; bicyclo-[2.2.1]heptan-2-yl; 2,3-dihydro-1H-indenyl; 1,2,3,4-tetrahydronaphthalenyl; C_{1-6}alkyl monosubstituted with phenyl, substituted phenyl, napthalenyl, thienyl, furanyl, C_{1-4}alkylfuranyl, C_{3-7}cycloalkyl, hydroxy, C_{1-4}alkyloxy or R^6 is a radical $-OR^7$ with R^7 being hydrogen , C_{1-6}alkyl, C_{3-6}alkenyl, phenylC_{3-6}alkenyl, C_{3-6}alkynyl, pyrimidinyl, diphenylmethyl, (1-C_{1-4}alkyl-4-piperidinyl), C_{1-6}alkyl substituted with halo, hydroxy, amino, mono- or di(C_{1-6}alkyl)amino, trifluoro-methyl, carboxyl, C_{1-6}alkyloxycarbonyl, phenyl, substituted phenyl, thienyl, furanyl, C_{1-4}alkylfuranyl, pyridinyl, phenoxy, phenylthio, 2,3-dihydro-1,4-benzo-dioxinyl, 1H-benzimidazolyl, C_{1-4}alkyl substituted 1H-benzimidazolyl, (1,1'-bi-phenyl)-4-yl or 2,3-dihydro-2-oxo-1H-benzimidazolyl; and R^8 is hydrogen.

11. A composition according to claim 1, substantially as hereinbefore described and exemplified.

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