USE OF AZOLE DERIVATIVES FOR THE TREATMENT OF INFLAMMATORY SKIN CONDITIONS

The present invention concerns a use of at least one azole derivative selected in the group consisting of bifonazole, butoconazole, chloridantoin, chlorimidazole, cicloconazole, clotrimazol, econazol, eponiconazole, fenticonazole, fluconazole, isooniconazole, ketoconazole, lanoconazole, miconazole, oniconazole, oxiconazole, sertaconazole, sulconazole, tioconazole, 2-benyl and triazole derivatives, for the preparation of a composition intended to combat the effects of free radicals.
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USE OF AZOLE DERIVATIVES FOR THE TREATMENT OF INFLAMMATORY SKIN CONDITIONS

The present invention relates to new uses of azole derivatives, more particularly in dermatological and/or cosmetological applications.

Among the attacks to which the body is subjected, free radicals represent a major source of harmful effects, in particular on the skin and mucous membranes. They result from the surrounding oxygen, which generates reactive radical forms. Mention may be made of the radical anion, the superoxide radical, the hydroxyl radical, nitric oxide (NO') or peroxides. They are involved in ageing mechanisms but also in irritation or hypersensitivity phenomena.

Products capable of combating their effects are thus actively sought after. Provision has thus been made to use antioxidizing inhibitors, such as, for example, vitamin C, glutathione or α-tocopherol. Another route has been the use of an enzyme, such as superoxide dismutase.

The Applicant Company has now found that azole derivatives exhibit an antiradical activity.

Azoles have been provided in particular as herbicides and in many applications as medicaments, in particular in hypertension, mood disorders, or as tranquillizers or antitumours. They have mainly been described as antibiotics and antifungals.

In the field of cosmetology, they have been introduced into compositions intended to combat dandruff or alopecia. Applications in the treatment of seborrhoeic skin, in combination with antiseptics, have been provided in WO 93 07847.
EP 396,184 relates to compositions containing a combination of ketoconazole and of a retinoid for treating hyperkeratoses.

EP 747,042 relates to combinations intended to improve the appearance of the skin, containing a combination of azole and of short-chain lipids, such as ceramides, in order to promote renewal of the keratinocytes and thus to prevent and decrease wrinkles.

The Applicant Company has now unexpectedly found that azole derivatives, by themselves, have an antiradical activity.

For this reason, the subject of the present invention is the use of at least one azole derivative for the preparation of a composition intended to combat the effects of free radicals.

Azoles are 5-membered heterocyclic compounds, at least one of the ring members of which is a nitrogen atom. The compounds suited to the invention are preferably imidazole or triazole derivatives and in particular compounds known for their antifungal activity.

Mention may be made, in a non-limiting way, of the compounds from the group comprising: bifonazole, butoconazole, chlordantoin, chlormidazole, cloconazole, clotrimazole, econazole, enilconazole, fenticonazole, flutrimazole, isoconazole, ketoconazole, lanoconazole, miconazole, omoconazole, oxiconazole, sertaconazole, sulconazole, tioconazole, fluconazole, itraconazole, saperconazole, terconazole or elubiol.

These compounds can be used alone or as a mixture, optionally in the form of their pharmaceutically or cosmetologically acceptable salts.
Compounds which are particularly suited to the implementation of the invention are elubiol, or ethyl cis-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazine-carboxylate, and ketoconazole.

For someazole derivatives, the compositions may be suited to administration by the oral route.

However, according to one of the preferred embodiments, the azoles are used to prepare a dermatological or cosmetological composition.

Such compositions can in particular be in the form of lotions, suspensions, solutions, gels, 0/W, W/O or multiple emulsions, creams, ointments or hydrogels or even in the solid form, as sticks or as powders.

The active products can also be encapsulated in carrier systems, such as liposomes or other microvesicles.

The compositions will thus contain dermatologically and/or cosmetologically acceptable excipients known to a person skilled in the art, such as fats or oils, texturizing agents, thickeners, emulsifiers, surfactants, buffer systems, preservatives, fragrances, dyes, pigments and the like.

The compositions can also contain moisturizing agents and/or agents for improving skin penetration.

The azoles can be combined, in the compositions according to the invention, with another active principle or another antiradical agent; the compositions can also contain sunscreens.

According to another aspect of the invention, the azoles as defined above are used for the preparation of a composition intended to combat inflammation.
This is because it could be demonstrated, in the context of the present invention, that azole derivatives not only have an inhibiting effect on the peroxidation of membrane lipids but also inhibit the production of NO by the cells.

Nitric oxide NO is an important physiological mediator, as vasodilator, neurotransmitter and proinflammatory agent. This oxygen derivative attests to attack on the cells, in particular by UV radiation. Its synthesis is mediated by NO synthase; it is then rapidly degraded to nitrites and nitrates. Spectrophotometric quantitative determination of the nitrites in the culture supernatant in the presence of the Griess reagent reveals the NO synthase activity.

Another aspect of the invention relates to the use of azole derivatives as described above for the preparation of a composition intended for the treatment of sensitive skin.

The problems of "sensitive" or "hyperreactive" skin affect an increasing number of children and adults.

The notion of sensitive skin covers a combination of manifestations comprising reactive skin and intolerant skin. Atopic skin may also be included. These skin types are sometimes improperly known as "allergic" by the subjects; however, while an allergic component can sometimes be evoked in the symptoms of a sensitive skin, it may not be limited to it. The triggering factors can be environmental attacks, such as wind, pollution, temperature variations, excessively hard water or ill-suited health, cosmetic or care products; these phenomena can also be associated with stress or emotions experienced by the subject, certain diets or
the taking of medicaments. There additionally exist individual (in particular neurological or hormonal) or hereditary predisposing factors which accentuate these reactions.

The subject generally experiences skin discomfort which can manifest itself by subjective and/or objective signs. The skin readily itches or smarts or experiences stabbing pains and there may be feelings of warmth, stinging or burning. The skin can redden or desquamate. Xerosis, seborrhoeic dermatitis, telangiectasias, blisters or even oedema is occasionally observed.

In more serious cases, dermatological conditions of immunoallergic type, such as atopy, eczema or neurodermatitides, may be observed.

This condition may be displayed on the skin, mucous membranes or scalp. In the latter case, it may be associated with a dandruff condition and/or alopecia.

The condition of this skin type can be improved by the application of compositions containing an azole derivative, optionally in combination with one or more other active principles, in particular soothing agents.

Compounds which are particularly preferred in the implementation of the invention are ketoconazole and elubiol. The synthesis of elubiol has been described in Patent US 4,335,125; it is a dichlorophenylimidazol-dioxolane derivative, known for its antifungal and antiseborrhoeic properties.

The concentration of azole derivative in the compositions is preferably between 0.0001% and 5% w/w, advantageously between 0.05% and 2% w/w, and, more preferably, between 0.5% and 1% w/w.
Finally, the invention also relates to a method for the cosmetic treatment of detrimental changes of the skin related to the activity of free radicals, characterized in that at least one azole derivative as described above is applied locally.

**Example 1: Inhibition of the peroxidation of lipids**

This is evaluated by quantitative determination of thiobarbituric acid, according to the following methodology.

Normal human skin fibroblasts, as a single layer, are exposed to oxidative stress by irradiation with UVA radiation. This irradiation generates reactive oxygen species, resulting in the peroxidation of the membrane lipids which can ultimately result in cell death. The peroxidation of the membrane lipids is evaluated by measuring the level of malondialdehyde (final product from the peroxidation of lipids) by quantitative determination of thiobarbituric acid (TBARS quantitative determination).

The cells are treated during the irradiation (simultaneous treatment).

The following products are tested:
- Elubiol, at 0.0001%, 0.0005% and 0.001%
- Ketoconazole, at 0.0001%, 0.0005% and 0.001%.

The elubiol and the ketoconazole are dissolved in ethanol, which has previously shown that it does not possess any antilipoperoxidation activity.
- α-Tocopherol, 0.004% (Positive control).

The products are tested during three experiments.

The experimental results are expressed as pmol of thiobarbituric acid/ml and as percentage inhibition. They are summarized in Table I:
Table I

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<tr>
<th>Products</th>
<th>TBARS (pmol/ml)</th>
<th>% inhibition</th>
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<tr>
<td>Control</td>
<td>1.68 ± 0.44</td>
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<tr>
<td>Control/UV</td>
<td>113.07 ± 3.80</td>
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<tr>
<td>α-Tocopherol/UV</td>
<td>66.75 ± 4.07</td>
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<td>Elubiol</td>
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<td>1 (0.0001%)/UV</td>
<td>84.38 ± 0.32</td>
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<td>2 (0.0005%)/UV</td>
<td>71.93 ± 4.08</td>
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<td>3 (0.001%)/UV</td>
<td>83.43 ± 2.56</td>
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<td>Ketoconazole</td>
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<td>1 (0.0001%)/UV</td>
<td>97.18 ± 1.97</td>
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<td>2 (0.0005%)/UV</td>
<td>63.60 ± 3.75</td>
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<td>3 (0.001%)/UV</td>
<td>55.93 ± 2.26</td>
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α-Tocopherol induces 41% inhibition of the production of TBARS, compared with the irradiated control. This result validates the test.

Elubiol, whatever the concentration tested, induces 25 to 36% inhibition of the production of TBARS.

Ketoconazole (from 0.0001% to 0.001%) induces a dose-dependent inhibition which reaches 50% inhibition for the highest concentration.

Ketoconazole and elubiol thus exhibit an antilipoperoxidation activity.

Example 2: Effect on the production of nitric oxide NO

RAW 264 cells, a macrophage-like mouse cell line, are stimulated by the combination of lipopolysaccaride
(1 μg/ml) and of interferon-γ (1000 U/ml) to induce the production of NO. At the same time, the cells are treated with the product under test at different concentrations. After incubating for 18 hours, the supernatants are harvested in order to evaluate the production of NO by spectrophotometric measurement of the nitrites (stable final product, originating from NO) by the Griess reaction.

The following products are tested:
- Elubiol, at 0.0001%, 0.0005% and 0.001% in ethanol
- Ketoconazole, at 0.0001%, 0.0005% and 0.001% in ethanol
- LNMMA, 1 mM = 0.025% (N-monomethyl-L-arginine).

Each measurement is carried out in triplicate.

The results are expressed as nitrite content (μM) and as percentage activity. The experimental results are summarized in the following table.

<table>
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<tr>
<th>Products</th>
<th>Nitrite (μM)</th>
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<tr>
<td>Control</td>
<td>31.30 ± 0.70</td>
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<td>LNMMA, 1 mM</td>
<td>10.54 ± 0.25</td>
<td>66.3% inhibition</td>
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<td>Elubiol</td>
<td>30.47 ± 0.21</td>
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<td>25.19 ± 0.70</td>
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<td></td>
<td>8.62 ± 0.41</td>
<td>72.5% inhibition</td>
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<td>Ketoconazole</td>
<td>33.33 ± 0.91</td>
<td>6.5% stimulation</td>
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<td>25.40 ± 0.28</td>
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<td>21.55 ± 0.59</td>
<td>31.2% inhibition</td>
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The LMMMA (positive control) induces 66.3% inhibition of the production of NO, with respect to the control. This result validates the experiment.

Elubiol and ketoconazole (at 0.005%) induce a similar inhibition of the production of NO (approximately 19% inhibition with respect to the control).

Elubiol at 0.001% induces 72.5% inhibition of the production of NO.

Ketoconazole at 0.001% induces 31.2% inhibition of the production of NO, without affecting the viability of the cells.

**Example 3: Composition**

```
- Purified water  q.s.p.
- Methyl p-hydroxybenzoate  0.30000
- PEG 6000 distearate  3.00000
- Oramix NS 10  1.00000
- Oramix CG 110  5.00000
- Glucamate DOE 120  2.00000
- Amonyl 675 SB  5.00000
- Glycerol  5.00000
- Texapon ASV  3.00000
- Salicylic acid  1.00000
- β-Glucan  0.20000
- D-Panthenol  2.00000
- Ketoconazole  0.80000
- B.H.T.  0.20000
- Anhydrous sodium sulphite  0.40000
- EDTA  0.10000
- DC green No. 5 W073 (0.1%)  0.30000
```
- DC yellow No. 10 W074 (0.1%)  0.10000
- Carbopol EDT 2020  0.20000
- Lipacid C8G  0.50000
- Na Citrate  0.40000
- Sodium hydroxide (10%)  2.00000
CLAIMS

1. Use of at least one azole derivative selected in the group consisting of bifonazole, butoconazole, chlordantoin, chlorimidazole, cloconazole, clotrimazole, econazole, enilconazole, fenticonazole, flutrimazole, isoconazole, ketoconazole, lanoconazole, miconazole, omoconazole, oxiconazole, sertaconazole, sulconazole, tioconazole, elubiol and triazole derivatives, for the preparation of a composition intended to combat the effects of free radicals.

2. Use according to Claim 1, characterized in that the azole derivative is a triazole derivative selected in the group consisting of fluconazole, itraconazole, saperconazole and terconazole.

3. Use of at least one azole derivative according to one of Claims 1 and 2, for the preparation of a dermatological or cosmetological composition.

4. Use of at least one azole derivative according to one of Claims 1 to 3, for the preparation of a composition intended to combat inflammation.

5. Use of at least one azole derivative according to one of Claims 1 to 4, for the preparation of a composition intended for the treatment of sensitive skin.

6. Use according to one of Claims 1 to 5, characterized in that the azole derivative is chosen from ketoconazole and elubiol.

7. Use of at least one azole derivative according to one of Claims 1 to 6, characterized in that the concentration of azole derivative in the composition is between 0.0001% and 5% w/w.
8. Method for the cosmetic treatment of detrimental changes of the skin related to the activity of free radicals, characterized in that at least one azole derivative as defined in Claims 1 and 2 is applied locally.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/415

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

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>FR 2 714 380 A (BIOXYTECH SA) 30 June 1995 see claims 1-4</td>
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<td>EP 0 312 960 A (MERRELL DOW PHARMACEUTICALS INC) 26 April 1989 see page 2</td>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:
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  "X" document of the same family

Date of the actual completion of the international search: 18 December 1998
Date of mailing of the international search report: 29/12/1998

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