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EUROPEAN PATENT APPLICATION

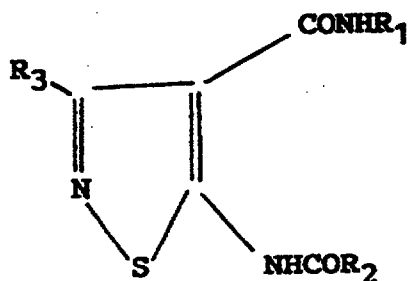
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NL PT SE(71) Applicant: Torf Establishment
Städtle 36
FL-9490 Vaduz(LI)(72) Inventor: Dubowska-Inglot, Anna, Prof.
Czarnieckiego 38/4
PL-53-651 Wrocław(PL)(74) Representative: Büchel, Kurt F., Dr.
Patentbüro Dr. Büchel Letzanaweg 25
FL-9495 Triesen (LI)(54) **Bioactive compositions and pharmaceutical preparations.**

(57) A bioactive composition comprises an isothiazole compound of the general formula I

**(I.)**

- wherein R₁ is halophenyl, R₂ is phenyl and R₃ is lower alkyl - and a peat-derived product containing not more than 70%, preferably not more than 60%, by weight, of inorganic salts, especially of sodium chloride, based on dry solids.

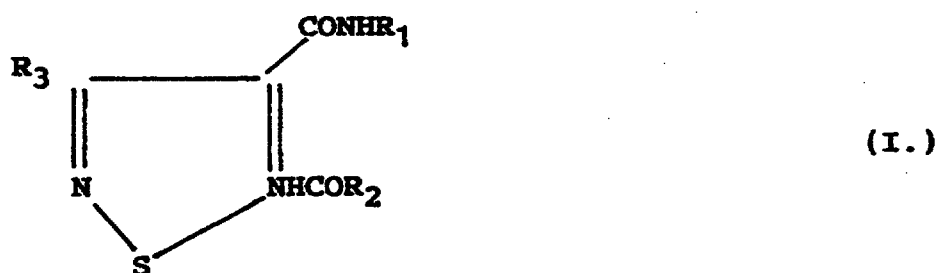
EP 0 540 945 A1

The present invention relates to bioactive compositions and to pharmaceutical preparations containing same. It is known that certain isothiazole derivatives, particularly amides of 5-aminoisothiazole-4-carboxylic acid, have anti-inflammatory activity comparable with the activity of non-steroidal anti-inflammatory drugs, such as indomethacin. These compounds are also known to possess antiviral, antibacterial and antimycotic activities. A typical representative of these isothiazole derivatives is the p-chlorophenylamide of 3-methyl-5-benzoyl-aminoisothiazole-4-carboxylic acid, also known as Vratizolin (R) (Arch. Immunol. et Ther. Exp. 1973, 21, 891).

On the other hand, peat extracts obtained by various methods using various extraction media are known to contain bioactive ingredients, which render such extracts useful for cosmetic and pharmaceutical purposes. (Chemical Abstracts 101(10), 78854e).

It has now been found that the combination of the above thiazole derivatives with certain peat extracts (peat-derived products) results in an antiviral and anti-inflammatory drug with increased therapeutic potential. Thus, the present invention relates to a bioactive composition which is characterized in that it comprises

a) an isothiazole compound of the general formula I

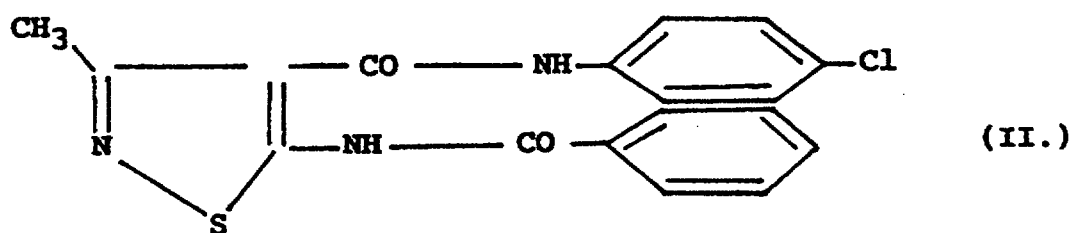


wherein R₁ is halophenyl, R₂ is phenyl and R₃ is lower alkyl, and

b) a peat-derived product containing not more than 70%, preferably not more than 60%, by weight, of inorganic salts, especially of sodium chloride, based on dry solids.

Preferred compositions according to the present invention are characterized in that the isothiazole compound a) is a compound of formula I, wherein R₁ is chlorophenyl, preferably p-chlorophenyl.

With respect to the substituent R₃ of the isothiazole compounds a), those compounds are preferred, wherein R₃ is methyl. The most preferred isothiazole compound a) is a compound of formula I, wherein R₁ is p-chlorophenyl, R₂ is phenyl and R₃ is methyl, i.e. the compound 3-methyl-5-benzoylamino-isothiazole-4-carboxy-p-chloro-phenylamide, also designated as vratizolin. This compound has the formula II



Vratizolin (R) is a registered trade mark in Poland. Further preferred compositions according to the present invention are characterized in that the peat-derived product is obtainable by a process wherein a highly concentrated solution of inorganic salts, especially of sodium chloride, containing peat-derived bioactive ingredients, is diluted with demineralized water and subjected to reverse osmosis in order to desalinate the solution, inorganic salts being removed, and wherein the resulting solution is concentrated and clarified, and, preferably, sterilized and/or spray-dried.

Peat-derived products of this type as well as their production are described in PCT Application No. PCT/EP92/00491 of 4th March, 1992.

A particularly preferred peat-derived product is the product TTP as specified in the above PCT Application and available from Torf Corporation, Wroclaw, ul. Mydlana 2, Poland. It is a spray-dried powder which is easily processable in forming pharmaceutical preparations. TTP stands for "TOLPA^(R) Torf



Preparation", TOLPA^(R) being a registered trade mark in Poland. The weight ratio of compound a) to compound b) in the compositions according to the present invention is about 30:1, preferably 30:2, more preferably 30:3.

The compositions according to the present invention are useful for producing pharmaceutical preparations according to conventional methods by mixing these compositions with pharmaceutically acceptable carriers. Accordingly, the present invention also relates to pharmaceutical preparations comprising a combination of an isothiazole compound as described above and a peat-derived product as described above, together with a pharmaceutically acceptable carrier material.

Such preparations may contain the active ingredient (i.e. the combination of peat-derived product and isothiazole compound) in a quantity of 3.1%, preferably 3.2%, more preferably 3.3% by weight. A preferred pharmaceutical preparation is one which contains Vratizolin (R) and TTP.

Vratizolin and related isothiazoles are not inducers of cytokines, such as interferons (IFN) and tumor necrosis factor (TNF). However, in the presence of IFN and TNF inducers they may stimulate the synthesis of such cytokines and prolong their action.

It was found that the above isothiazole derivatives, such as vratizolin, administered together with the above peat-derived products, such as TTP, in human peripheral blood leukocyte cultures potentiate the activity of the peat-derived product in the production of IFN and TNF. The combination of the two components a) and b) in the composition according to the present invention was found to be clearly synergistic.

Pharmaceutical preparations according to the present invention, i.e. Preparations comprising the components a) and b) are useful for the treatment of herpes virus infections of the skin or mucous membranes (e.g. H. simplex labialis, facialis, H. genitalis, H. zoster varicella, eczema herpetica, other viral infections of mucous membranes, and various inflammatory skin diseases).

Pharmaceutical preparations according to the present invention i. e. Preparations comprising the components a) and b) are particularly useful for the treatment of genital virus infections transmitted during sexual intercourse and also for the prophylaxis of HIV infections together with condoms.

Examples of pharmaceutical preparations are:

30

1.	Vratizolin (R)	0.10
	TTP	0.01
	Vehiculum	ad 10.00

The hydrophilic vehiculum for the treatment of mucous membrane infections is qualitatively composed e.g. of the following ingredients: polyethylene glycol 300, glycerin, polyethylene glycol 4000, and Tween 80) or Oral base^R Plain Colgate - Hoyt Labs.

Div. of Colgate - Palmolive Comp.

One Colgate Way, Canton, WA 02021 USA (ingredients: pectin, sodium carboxymethylcellulose, and plasticized hydrocarbon gel).

The vehiculum for the treatment of skin infections is hydrophilic, with following ingredients: polyethylene glycol 300, glycerin, polyethylene glycol 4000, and Tween 80.

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2.	Vratizolin	1.50
	TTP	0.05
	Vehiculum	ad 50.00

The vehiculum for the treatment and prevention of genital and oral virus infections is as quoted above.

50 Claims

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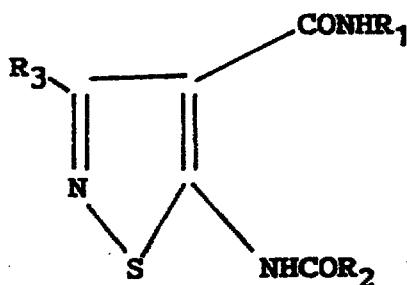
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(I.)

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b) peat-derived product containing not more than 70%, preferably not more than 60%, by weight, of inorganic salts, especially of sodium chloride, based on dry solids.

2. A composition as claimed in Claim 1, characterized in that the isothiazole compound a) is a compound of formula I, wherein R_1 is chlorophenyl, preferably p-chlorophenyl.
3. A composition as claimed in Claim 1 or 2 characterized in that the isothiazole compound a) is a compound of formula I, wherein R_3 is methyl.
4. A composition as claimed in any one of Claims 1 to 3, characterized in that the isothiazole compound a) is a compound of formula I, wherein R_1 is p-chlorophenyl, R_2 is phenyl and R_3 is methyl, i.e. the compound 3-methyl-5-benzoylaminoisothiazole-4-carboxy-p-chloro-phenylamide, designated as vrazizolin.
5. A composition as claimed in anyone of Claims 1 to 4, characterized in that the peat-derived product b) is a product obtainable by a process, wherein a highly concentrated aqueous solution of inorganic salts, especially of sodium chloride, containing peat-derived bioactive ingredients, is diluted with de-mineralized water and subjected to reverse osmosis in order to desalinate the solution, inorganic salts being removed, and wherein the resulting solution is concentrated and clarified, and, preferably, sterilized and/or spray-dried.
6. A composition as claimed in any one of Claims 1 to 5, characterized in that the peat-derived product b) is a product as specified in PCT application PCT/EP92/00491.
7. A composition as claimed in any one of Claims 1 to 6, characterized in that the peat-derived product b) is TTP, as specified in PCT application PCT/EP92/00491.
8. A composition as claimed in anyone of Claims 1 to 7, characterized in that the weight ratio of product a) and compound b) is 30:1, preferably 30:2, more preferably 30:3.
9. A pharmaceutical preparation, characterized in that it contains, as active ingredient, a composition as claimed in anyone of Claims 1 to 8, together with a pharmaceutically acceptable carrier material.
10. A pharmaceutical preparation, as claimed in Claim 9, characterized in that the active ingredient is a combination of Vratizolin (R) and TTP.
11. A pharmaceutical preparation as claimed in Claim 9 or 10, characterized in that it contains the active ingredient in a quantity of 3.1%, preferably 3.2%, more preferably 3.3% by weight.

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☒ Claim(s) : paged6 to paged7
☐ Drawing(s) : paged to paged
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☒ Description : paged1 to paged5
☒ Claim(s) : paged6 to paged7
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BIOACTIVE COMPOSITIONS AND PHARMACEUTICAL PREPARATIONS

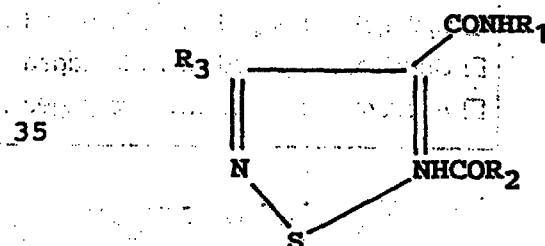
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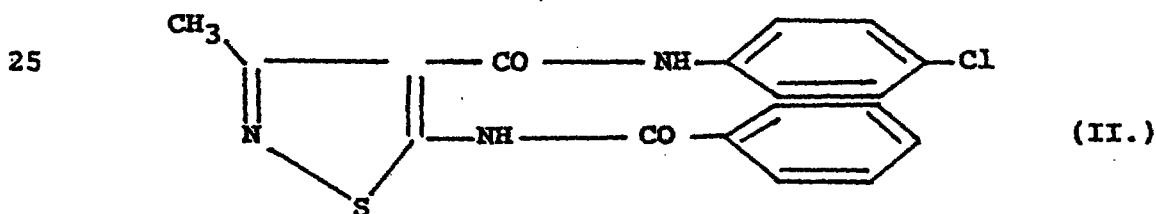


wherein R_1 is halophenyl, R_2 is phenyl and R_3 is lower alkyl, and

5 b) a peat-derived product containing not more than 70%, preferably not more than 60%, by weight, of inorganic salts, especially of sodium chloride, based on dry solids.

Preferred compositions according to the present invention
10 are characterized in that the isothiazole compound a) is a compound of formula I, wherein R_1 is chlorophenyl, preferably p-chlorophenyl.

With respect to the substituent R_3 of the isothiazole
15 compounds a), those compounds are preferred, wherein R_3 is methyl. The most preferred isothiazole compound a) is a compound of formula I, wherein R_1 is p-chlorophenyl, R_2 is phenyl and R_3 is methyl, i.e. the compound 3-methyl-5-benzoylamino-isothiazole-4-carboxy-p-chloro-phenylamide,
20 also designated as vratizolin. This compound has the formula II



Vratizolin (R) is a registered trade mark in Poland. Further preferred compositions according to the present invention are characterized in that the peat-derived product is
35 obtainable by a process wherein a highly concentrated solution of inorganic salts, especially of sodium chloride, containing peat-derived bioactive ingredients, is diluted with demineralized water and subjected to reverse osmosis in



order to desalinate the solution, inorganic salts being removed, and wherein the resulting solution is concentrated and clarified, and, preferably, sterilized and/or spray-dried.

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Peat-derived products of this type as well as their production are described in PCT Application No. PCT/EP92/00491 of 4th March, 1992.

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15 Preparation", TOLPA(R) being a registered trade mark in Poland. The weight ratio of compound a) to compound b) in the compositions according to the present invention is about 30:1, preferably 30:2, more preferably 30:3.

- 20 The compositions according to the present invention are useful for producing pharmaceutical preparations according to conventional methods by mixing these compositions with pharmaceutically acceptable carriers. Accordingly, the present invention also relates to pharmaceutical
25 preparations comprising a combination of an isothiazole compound as described above and a peat-derived product as described above, together with a pharmaceutically acceptable carrier material.

- 30 Such preparations may contain the active ingredient (i.e. the combination of peat-derived product and isothiazole compound) in a quantity of 3.1%, preferably 3.2%, more preferably 3.3% by weight. A preferred pharmaceutical preparation is one which contains Vratizolin (R) and TTP.

35

Vratizolin and related isothiazoles are not inducers of cytokines, such as interferons (IFN) and tumor necrosis

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factor (TNF). However, in the presence of IFN and TNF inducers they may stimulate the synthesis of such cytokines and prolong their action.

- 5 It was found that the above isothiazole derivatives, such as
vratizolin, administered together with the above peat-
derived products, such as TTP, in human peripheral blood
leukocyte cultures potentiate the activity of the peat-
derived product in the production of IFN and TNF. The
10 combination of the two components a) and b) in the
composition according to the present invention was found to
be clearly synergistic.

- Pharmaceutical preparations according to the present
15 invention, i.e. Preparations comprising the components a)
and b) are useful for the treatment of herpes virus
infections of the skin or mucous membranes (e.g. H. simplex
labialis, facialis, H. genitalis, H. zoster varicella,
eczema herpetica, other viral infections of mucous
20 membranes, and various inflammatory skin diseases.

- Pharmaceutical preparations according to the present
invention i. e. Preparations comprising the components a)
and b) are particularly useful for the treatment of genital
25 virus infections transmitted during sexual intercourse and
also for the prophylaxis of HIV infections together with
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Examples of pharmaceutical preparations are:

30

1.	Vratizolin (R)	0.10
	TTP	0.01
	Vehiculum	ad 10.00

- 35 The hydrophilic vehiculum for the treatment of mucous
membrane infections is qualitatively composed e.g. of the

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following ingredients: polyethylene glycol 300, glycerin, polyethylene glycol 4000, and Tween 80)

or Oral base^R Plain Colgate-Hoyt Labs.

Div. of Colgate-Palmolive Comp.

5 One Colgate Way, Canton, WA 02021 USA

(ingredients: pectin, sodium carboxynethylcellulose, and plasticized hydrocarbon gel).

10 The vehiculum for the treatment of skin infections is hydrophilic, with following ingredients:
polyethylene glycol 300, glycerin, polyethylene glycol 4000, and Tween 80.

2.	Vratizolin	1.50
15	TTP	0.05
	Vehiculum	ad 50.00

The vehiculum for the treatment and prevention of genital and oral virus infections is as quoted above.

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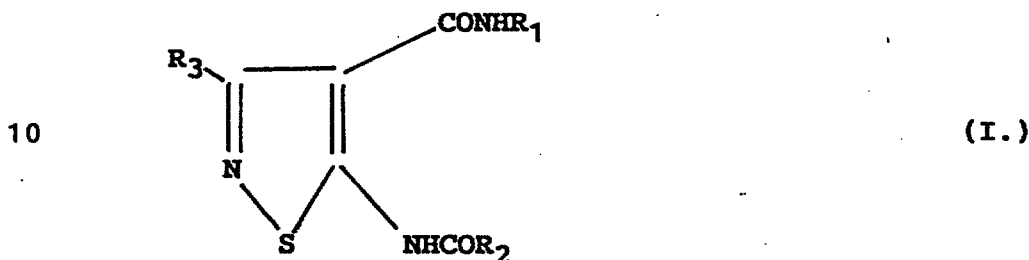
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CLAIMS

1. Bioactive composition, characterized in that it comprises
a) an isothiazole compound of the general formula I

5



- 15 wherein R_1 is halophenyl, R_2 is phenyl and R_3 is lower alkyl and

- b) peat-derived product containing not more than 70%, preferably not more than 60%, by weight, of inorganic salts, especially of sodium chloride, based on dry
20 solids.

2. A composition as claimed in Claim 1, characterized in that the isothiazole compound a) is a compound of formula I, wherein R_1 is chlorophenyl, preferably p-chlorophenyl.
3. A composition as claimed in Claim 1 or 2 characterized in that the isothiazole compound a) is a compound of
25 formula I, wherein R_3 is methyl.
4. A composition as claimed in any one of Claims 1 to 3, characterized in that the isothiazole compound a) is a compound of formula I, wherein R_1 is p-chlorophenyl, R_2
30 is phenyl and R_3 is methyl, i.e. the compound 3-methyl-5-benzoylaminoisothiazole-4-carboxy-p-chloro-phenylamide, designated as vratizolin.
5. A composition as claimed in anyone of Claims 1 to 4, characterized in that the peat-derived product b) is a

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- product obtainable by a process, wherein a highly concentrated aqueous solution of inorganic salts, especially of sodium chloride, containing peat-derived bioactive ingredients, is diluted with demineralized water and subjected to reverse osmosis in order to desalinate the solution, inorganic salts being removed, and wherein the resulting solution is concentrated and clarified, and, preferably, sterilized and/or spray-dried.
- 5
- 10 6. A composition as claimed in any one of Claims 1 to 5, characterized in that the peat-derived product b) is a product as specified in PCT application PCT/EP92/00491.
7. A composition as claimed in any one of Claims 1 to 6, characterized in that the peat-derived product b) is TTP,
- 15 as specified in PCT application PCT/EP92/00491.
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- 20 9. A pharmaceutical preparation, characterized in that it contains, as active ingredient, a composition as claimed in anyone of Claims 1 to 8, together with a pharmaceutically acceptable carrier material.
- 25 10. A pharmaceutical preparation, as claimed in Claim 9, characterized in that the active ingredient is a combination of Vratizolin (R) and TTP.
- 30 11. A pharmaceutical preparation as claimed in Claim 9 or 10, characterized in that it contains the active ingredient in a quantity of 3.1%, preferably 3.2%, more preferably 3.3% by weight.

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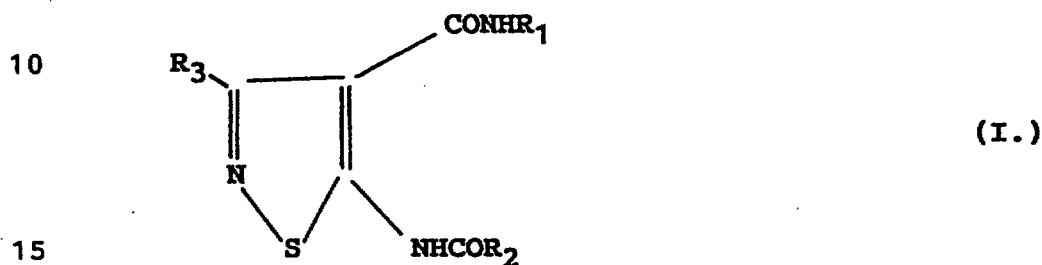
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BIOACTIVE COMPOSITIONS AND PHARMACEUTICAL PREPARATIONS

Abstract

5 A bioactive composition comprises an isothiazole compound of the general formula I



- wherein R₁ is halophenyl, R₂ is phenyl and R₃ is lower alkyl - and a peat-derived product containing not more than 70%, preferably not more than 60%, by weight, of inorganic salts, especially of sodium chloride, based on dry solids.

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☒	Description : paged 1... to paged 5...	
☒	Claim(s) : paged 6... to paged 7...	
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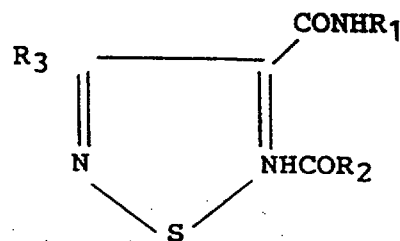
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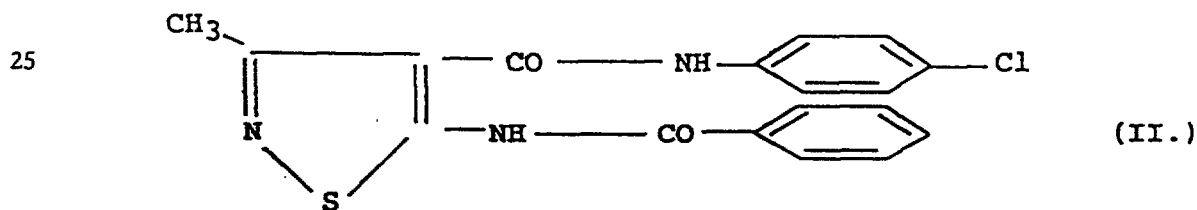
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10 combination of the two components a) and b) in the composition according to the present invention was found to be clearly synergistic.

Pharmaceutical preparations according to the present
15 invention, i.e. preparations comprising the components a) and b) are useful for the treatment of herpes virus infections of the skin or mucous membranes (e.g. H. simplex labialis, facialis, H. genitalis, H. zoster varicella, eczema herpetica, other viral infections of mucous
20 membranes, and various inflammatory skin diseases.

Pharmaceutical preparations according to the present invention i.e. preparations comprising the components a) and b) are particularly useful for the treatment of genital
25 virus infections transmitted during sexual intercourse and also for the prophylaxis of HIV infections together with condoms.

Examples of pharmaceutical preparations are:

30

1.	Vratizolin ^(R)	0.10
	TTP ^(R)	0.01
	Vehiculum	ad 10.00

35 The hydrophilic vehiculum for the treatment of mucous membrane infections is qualitatively composed e.g. of the

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following ingredients: polyethylene glycol 300, glycerin, polyethylene glycol 4000, and Tween[®] 80 or ORABASE[®] Plain der Firma Colgate-Hoyt Labs., Div. of Colgate-Palmolive Comp., One Colgate Way, Canton, WA 02021 USA

- 5 (ingredients: pectin, sodium carboxymethylcellulose, and plasticized hydrocarbon gel).

The vehiculum for the treatment of skin infections is
10 hydrophilic, with following ingredients:
polyethylene glycol 300, glycerin, polyethylene glycol 4000, and Tween 80.

2.	Vratizolin ^(R)	1.50
15	TTP ^(R)	0.05
	Vehiculum	ad 50.00

The vehiculum for the treatment and prevention of genital and oral virus infections is as quoted above.

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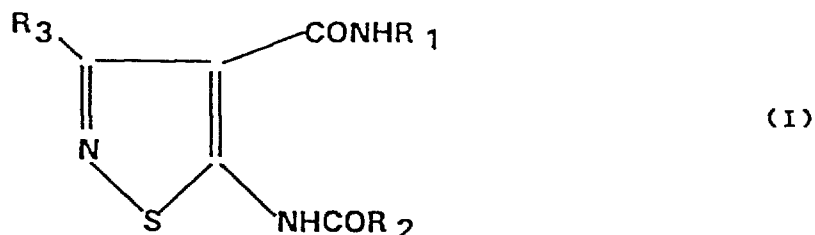
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CLAIMS

1. Bioactive composition, characterized in that it
5 comprises
a) an isothiazole compound of the general formula I



wherein R₁ is halophenyl, R₂ is phenyl and R₃ is lower alkyl and

- 10 b) a peat-derived bioactive product containing not more than 70%, preferably not more than 60%, by weight, of inorganic salts, especially of sodium chloride, based on dry solids.
2. A composition as claimed in claim 1, wherein R₁ of
15 compound a) is chlorophenyl, preferably p-chlorophenyl.
3. A composition as claimed in claim 1 or 2, wherein R₃ of compound a) is methyl.
4. A composition as claimed in any one of claims 1 to 3, wherein R₁ of compound a) is p-chlorophenyl, R₂ is phenyl
20 and R₃ is methyl, the compound thus being 3-methyl-5-benzoylaminoisothiazole-4-carboxy-p-chloro-phenylamide (Vratizolin).
5. A composition as claimed in any one of claims 1 to 4, characterized in that the peat-derived product b) is a
25 product obtainable by a process, wherein a highly concentrated aqueous solution of inorganic salts, especially of sodium chloride, containing peat-derived bioactive ingredients, is diluted with demineralized

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water and subjected to reverse osmosis in order to desalinate the solution, inorganic salts being removed, and wherein the resulting solution is concentrated and clarified, and, preferably, sterilized and/or spray-dried.

- 5 6. A composition as claimed in any one of claims 1 to 5, characterized in that the peat-derived product b) is a bioactive peat extract, preferably in the form of a spray-dried powder.
- 10 7. A composition as claimed in any one of claims 1 to 6, characterized in that the weight ratio of compound a) and product b) is 30:1, preferably 30:2, more preferably 30:3.
8. A composition according to any one of claims 1 to 7, characterized in that it further contains a pharmaceutically acceptable carrier material.
- 15 9. A composition as claimed in any one of claims 1 to 8, characterized in that it contains 3-methyl-5-benzoylaminoisothiazole-4-carboxy-p-chloro-phenylamide (Vratizolin) and a bioactive peat extract as defined in claim 6.
- 20 10. A composition as claimed in claim 8 or 9, characterized in that it contains compound a) and product b) in a total quantity of 3.1%, preferably 3.2%, more preferably 3.3% by weight.
- 25 11. A composition according to any one of claims 1 to 10, for use as a medicament.

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