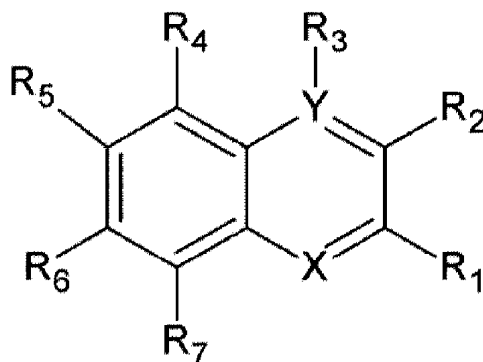




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(54) Titre : PREPARATION ANTIBACTERIENNE ET ANTIFONGIQUE CONTENANT UN COMPOSE D'ACIDEQUINOLEINE-2,3-DICARBOXYLIQUE ET SUPPORTS ORGANIQUES ET/OU INORGANIQUES
(54) Title: ANTIBACTERIAL AND ANTIFUNGAL PREPARATION CONTAINING A QUINOLINE-2,3-DICARBOXYLIC ACID COMPOUND AND ORGANIC AND/OR INORGANIC FILLERS



(57) **Abrégé/Abstract:**

The subject of the invention is an antibacterial and antifungal preparation constituting an additive to various materials, in particular, to plastics, containing no nanometal particles, which may be combined with almost any kind of polymers or other materials, from biodegradable polymer packaging, textiles, paints, to hardened PVC, using any processing technology, such as: extrusion, injection moulding, blowing, pressing, lamination, pouring or pumping through capillaries in production of continuous fibre for the textile industry. The antibacterial and antifungal preparation contains an active ingredient in the form of a derivative of an acid of the formula,

(see above formula)

where R₁ and R₂ signify, both jointly, carboxyl groups (-COOH), R₃, R₄, R₅, R₆, R₇ signify hydrogen (H), X signifies carbon (C) and Y signify nitrogen (N) or X signifies nitrogen (N) and Y signifies carbon (C) in the amount of 60 to 85% by weight, and the remaining amount is a composition of inorganic and/or organic fillers.

**ANTIBACTERIAL AND ANTIFUNGAL PREPARATION CONTAINING
A QUINOLINE-2,3-DICARBOXYLIC ACID COMPOUND AND ORGANIC AND/OR
INORGANIC FILLERS**

FIELD OF THE INVENTION

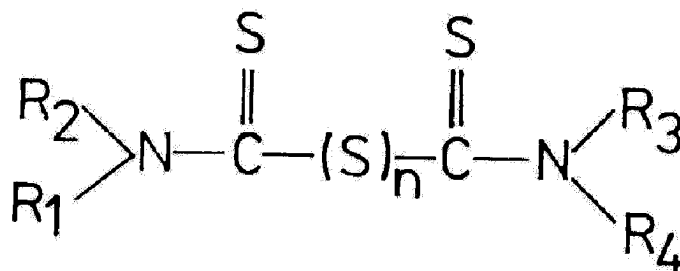
The subject of the invention is a preparation of organic origin, constituting an additive to materials and products requiring antibacterial and antifungal properties, not containing any nanometal particles. The developed preparation may be combined with almost every kind of polymers and other materials – from biodegradable polymer packaging, textiles, paints, to hardened PVC – using any processing technology, such as: extrusion, injection molding, blowing, pressing, lamination, pouring or pumping through capillaries in production of continuous fibre for the textile industry. The preparation is supposed to be added, for example, to plastics used for manufacturing of antimicrobial medical devices, vacuum containers for storage of food, packaging for foodstuffs, sealed vacuum packaging, kitchen cutting boards. It may also be used for manufacturing of other kitchen utensils, household appliances, air conditioners, water treatment devices, toys, for production of automobile components, office products, or clothing products and footwear. It may constitute an additive to paints, varnishes, textiles and other similar products. The invention also discloses the active ingredient utilized in the preparation.

BACKGROUND OF THE INVENTION

Known from the German patent description with the application number DE I 932 415 (application of 26 June 1969), is an invention disclosing a new group of molecular compounds of salts formed as a result of addition of sorbic acid, which may be formed through connection with a molecule of chlorine, bromine or iodine. The substance described therein has fungicidal and yeasticidal properties, utilized in protection of fruit trees and seeds as well as foodstuffs.

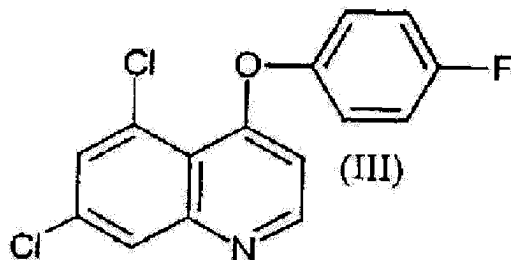
An invention is also known from the English patent description EN-988,483 (claim of 11 February 1963), disclosing sulphate salt of 5-methyl-8-hydroxy-quinoline. It is obtained as a solution of sulphate in a solution of hydrochloric acid and quinoline. This substance has bacteriostatic and bactericidal properties.

Another invention "Mould Control Agent" is known from the Polish patent description, patent no. PL-187979 (published: BUP 18/1999 of 30 August 1999), disclosing a mould control agent containing, as the biologically active ingredient, a mixture of copper bis (8-quinolinolate) in the amount of 5 to 80% by weight with a bis-thiocarbamyl polysulphide derivative with a formula shown in the drawing, where R₁, R₂, R₃ and R₄ are identical and signify a methyl or ethyl group, and "n" signifies an integer "1" or "2", particularly with tetramethylthiuram disulphide in the amount of 20 to 95% by weight.



The agent may be applied as an additive to finishing materials in the construction industry.

Another solution has been known, disclosed in a description of the Polish patent claim P-355623 (published: BUP 9/2004 of 4 May 2004) "Combinations of fungicidal active ingredients". The fungicide presented therein contains a combination of active ingredients, consisting of A) 8-t-butyl-2-(N-ethyl-N-n-propylamine)metylo-1,4-dioxaspiro[5,4]decan with a formula (1) (=spiroxamine) and B) 1-(4-chlorophenyl)-4,4-dimethyl-3-(1,2,4-triazol-1-ylmethyl)pentan-3-ol with a formula (II) (= tebuconazole) as well as C) 5,7-dichloro-4-(4-fluorophenoxy)quinoline with a formula (III) (= quinoxyfen).



Known from the US patent description, patent no. US 4,789,692 (Appl. No. 897,760), is an invention "Resin-immobilized biocides" disclosing a solid biocide resin concentrate for supplying to an end use resin composition, of which a primary thermoplastic resin comprises a major proportion, comprising a biocide in an amount which is effective to protect the resin composition from an microorganism attack, the solid biocidal resin concentrate comprising a first thermoplastic resin identical to or substantially identical to said primary thermoplastic resin, said primary thermoplastic resin being incompatible with stable incorporation of said biocide at 20 times end use concentration, an alloyed second thermoplastic resin and a biocide, selected from the group consisting of 10,10-oxybisphenoxazine and its derivatives, N(2-methyl-1-naphthyl) maleimide and 2-octyl-4-isothiazolin-3-one, stably incorporated and immobilized in the said alloyed resins at a concentration of at least 20 times end use concentration. Said first thermoplastic resin is selected from the group consisting polyethylene, nylon, polystyrene, polyvinyl chloride, polycarbonates, polypropylene, polyvinyl chloride/polyvinyl acetate copolymer, polyvinyl, acetate, polymethyl and methacrylate, and if said first thermoplastic resin is polyethylene, said second resin is selected from the group consisting of ethylene/acrylic acid copolymer, polypropylene, polystyrene, polyvinyl chloride/polyvinyl acetate copolymer, polyacrylic acid, ethylene/vinyl acetate/carbon monoxide terpolymer; and if the first thermoplastic resin is selected from the group consisting of nylon, polystyrene, polyvinyl chloride, polycarbonate, polypropylene, polyvinyl chloride/polyvinyl acetate copolymer, polyvinyl acetate, polymethyl methacrylate, said second thermoplastic resin is selected from the group consisting of ethylene/acrylic acid copolymer and ethylene/vinyl acetate/carbon monoxide terpolymer.

Known from US patent description US 7,361,719 (Appl. No. 503,040), is an invention “Monomer with anti-microbial character, polymer using the same, and manufacturing method thereof”, disclosing an anti-microbial acrylic copolymer with a molecular weight of 10 000 – 1 000 000, described with the formula disclosed in the invention; whereas, one of substituents in this case is a C1-C13 alkane group comprising one or more selected from the group consisting of esters, carbonyl group, amide, amine, cycloalkyls, ether, hydroxyl group, carboxylic acid, C2-C10 hetero ring containing N or O, sulpho group, silane, lactone and aldehyde groups.

Another antibacterial agent, containing a quinoline derivative, was described in a US paper published in the “Journal of Mononuclear Science part B: PHYSICS” (No. 48: 755-765, 2009 ISSN 00222348, print: N5 25 — 609 IX) “Effects of Anti-Bacterial Agents, Sample Preparation and Contact Time on Anti-Bacterial Efficacy in MDPE Film”. It discussed the antibacterial efficacy of medium-density polyethylene (MDPE) with various contents of different antibacterial agents, depending on the antibacterial concentration, size and form of the sample, MDPE, and the contact time, whereas three different of antibacterial agents were used, namely: (a) carbendazim and zinc dimethyl dithiocarbamate, (b) 2-hydroxypropyl-3-piperazinyl-quinoline carboxylic acid methacrylate and silver substituted zeolite. In order to assess the antibacterial efficacy, the most widespread microbes, Escherichia coli (E. Coli) ATCC 29214 and Staphylococcus aureus (S.aureus) ATCC 73565, were selected as Gram-negative and Gram-positive.

In June 2011, during the International Conference on Material Processing Technology (2011, June 2-3, Phuket, THAILAND), materials have been presented concerning assessment of mechanical and antibacterial properties of silicone rubber mixtures with an addition of the BIOCLEANCT substance: (2-Hydroxypropyl-3-Piperazinyl-Quinoline-Carboxylic Acid Methacrylate [HPQM]), displaying bactericidal and fungicidal properties.

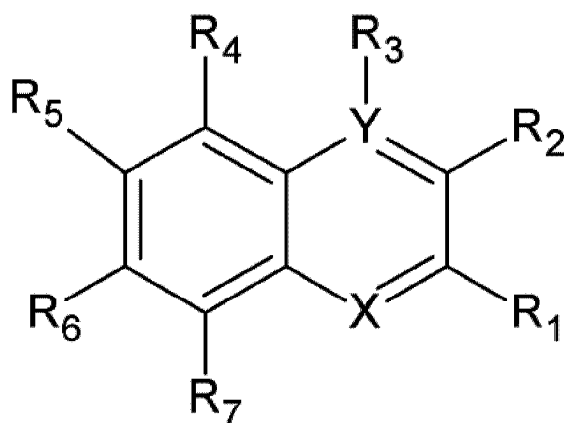
Biostatic agents, sometimes referred to as “antimicrobials”, will be used in many applications of plastics and in various industries. Products containing a bacteriostatic additive are characterized by many advantages, the most important of which is prevention of development of fungi and bacteria. The increasing possibilities

for spread of diseases create demand for antibacterial chemicals for use in industry, medicine and consumer goods, as well as in the food industry. The problem so far was development of a preparation which would reduce transmission of infectious diseases and bacteria or various fungi types, and would simultaneously not contain any toxic substances harmful to health. The known and used preparations release toxic chemical compounds which may cause cancer and infertility. The increasing easiness of transmission of diseases increases the risk of spread thereof and necessitates development of substances inhibiting this phenomenon. Efforts oriented towards containing the transmission of infectious diseases (including AIDS) provide a stimulus for search for increasingly new and more efficient agents to protect the universally used substances and materials as well as food.

The goal of the invention is to develop a preparation with antibacterial and antifungal properties, which will have no harmful properties of substances known hitherto, often containing nanometal particles, and simultaneously, a preparation containing a substance with antibacterial and antifungal properties, which may be incorporated in various substances: plastics, resins, fibers, paints, varnishes, protective preparations, as well as other substances at various processing stages.

SUMMARY OF THE INVENTION

During the conducted research, it was incidentally stated that an agent containing a derivative of 2,3-quinoline dicarboxylic acid with a formula shown below:



where R₁ and R₂ signify, both jointly, carboxyl groups (-COOH), R₃, R₄, R₅, R₆, R₇ signify hydrogen (H), X signifies carbon (C) and Y signifies nitrogen (N) or X signifies

nitrogen (N) and Y signifies carbon (C) – is a perfect antibacterial and antifungal agent, stable over time, effective already at small doses, and compatible with a multitude of types of plastics and other materials or compositions thereof.

The active ingredient will be known under the trade name “SEANTEX”.

The antibacterial and antifungal preparation containing, beside the biologically active ingredient used as antibacterial and antifungal ingredient, auxiliary ingredients in the form of fillers, is characterized in that it contains a biologically active ingredient being a derivative of the acid of the above formula, in which R₁ and R₂ signify, both jointly, carboxyl groups (-COOH), R₃, R₄, R₅, R₆, R₇ signify hydrogen (H), X signifies carbon (C) and Y signifies nitrogen (N) or X signifies nitrogen (N) and Y signifies carbon (C) in the amount of 60 to 85% by weight, and the remaining amount is a composition of inorganic and/or organic fillers.

Preferably, benzoic acid, sodium benzoate and/or curcumin are used as organic fillers in the preparation.

Preferably, chalk and silica are used as inorganic fillers in the preparation.

The preparation is preferably a part of a composition of plastics in an amount of 3-7% by mass.

The preparation is preferably a part of a composition of interior and exterior paints, varnishes and impregnations in the amount of 3-7% by mass.

The preparation is preferably a part of a composition of silicones and resins in the amount of 3-7% by mass.

DETAILED DESCRIPTION OF THE INVENTION

The preparation, according to the invention, contains 60 to 85% by weight of the active ingredient, and the remaining amount of the preparation comprises a composition of organic and inorganic fillers, namely, benzoic acid, sodium benzoate, curcumin, chalk, silica.

Curcumin is an organic chemical compound built of two feruloyl moieties connected with a carbon atom.

The developed antibacterial and antifungal preparation, is a biostatic additive of organic origin, containing no toxic compounds. The preparation satisfies the demand for products with an antibacterial effect, not containing any nanometal particles. This

preparation inhibits the development of microorganisms. The conducted research has shown that the products manufactured using the developed agent effectively prevent the development of known bacteria, such as *Bacillus subtilis*, *Escherichia coli*, *Proteus mirabilis*, *Proteus vulgaris*, *Streptococcus pneumoniae*, *Salmonella* and many others, as well as fungi: *Candida albicans*, *Aspergillus niger*, *Penicillium ochrochloron*, and many others. Another advantage of the developed preparation is easiness of use, non-toxicity, excellent mechanical properties, as well as compatibility with new generation biodegradable plastics. This preparation is tolerant to heat. The application of the developed preparation enables prevention of stains and discolouration of coloured materials, caused by microorganisms, and inhibits the development and spread of substances causing an unpleasant smell and loss of the desired mechanical properties in industrial and commercial products. The developed compound may be used in any thermoplastic material forming method and added to any material processing device without a necessity of additional expansion or installation of additional equipment. Such simple integration with the already existing material production processes eliminates barriers for introduction of the developed preparation to the already implemented production without a necessity to make the production process more expensive.

An important advantage of the described composition — due to its possibility of being internally incorporated into the structure of a polymer — is the fact that this agent is environmentally neutral, both during its incorporation into polymers, e.g. thermoplastic ones, in the form of so-called masterbatch, and in the production process or during recycling. It is capable of being used to protect various thermoplastic polymers of LDPE, MDPE, HDPE, PP, P5, rubber, PCV, PLA, PET and others against *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATC 25 923) and other bacteria.

The preparation is characterized by considerable antibacterial efficacy, lack of nanometals and halogens, as well as the fact that an addition of this agent does not cause any reduction of whiteness index of the material, nor does it prevent colouring thereof.

A relatively low melting point of the active ingredient and a high boiling point facilitates application of the preparation in many market products.

Materials containing the preparation according to the invention are recyclable.

The invention has been disclosed in embodiments which, however, only illustrate the invention, not limiting the possible applications thereof.

Embodiment no. 1

A preparation containing 80% of the substance disclosed in the invention and 20% of inorganic fillers – chalk and silica in a ratio of 1:1. A preparation with such composition is added to latex paints in the amount of 5% per unit of mass, and the entire composite is mixed until totally homogenous.

Latex paints containing the preparation according to the invention are resistant to the effect of fungi and bacteria.

Tests for resistance to development of fungi and bacteria were carried out in accordance with Work Instruction JA/0074/R based on the methodology described in the standard ISO 22196.

The following samples were subject to analyses:

- sample “0” – reference paint;
- sample “1” – paint into which 3% of the preparation was introduced;
- sample “2” – paint into which 5% of the preparation was introduced.

Testing method:

Suspensions of strains were applied to samples with dimensions of 5x5 cm. The suspensions on the samples were covered by pieces of sterile PE foil with dimensions of 4x4 cm in order to spread the microorganisms evenly. The samples were incubated for 24h at a temperature of 36°C for bacteria and at a temperature of 22°C for mould. Immediately after the inoculation of the samples, suspension was rinsed from a part of the samples of the reference sample in order to determine the number of cells/spores at a time of 0 h. A similar procedure was followed after 24 hours of contact with the remaining samples of the reference sample and the tested sample.

The results were presented in tables below, by calculating the difference of logarithms from the number of cfu/ml recovered from the reference sample and the tested sample after the contact time.

Test results and assessment with requirements

- *Log₁₀ Reduction* – a difference between the logarithm of the average cfu number on the reference samples after 24 h and the logarithm of the average cfu number on the tested samples.

Bacterial strain – *Staphylococcus aureus*

Sample	Repetition	Cell count /cm ³	Geom. mean of Cell count /cm ³	Log ₁₀ of Cell count /cm ²	Average Log ₁₀ of Cell count /cm ²	Log ₁₀ Reduction
	1	1,7E+0,4		4,23		
Ref.	2	1,5E+0,4	1,4E+0,4	4,17	4,16	
t=0h	3	1,2E+0,4		4,09		
	1	5,0E+0,4		4,70		
Ref.	2	6,3E+0,4	6,35E+0,4	4,80	4,80	
24h	3	8,3E=0,4		4,92		
	1	<1,0E+0,1		1,00		
Sample 1	2	<1,0E+0,1	<1,0E+0,1	1,00	1,00	3,80
	3	<1,0E+0,1		1,00		
	1	<1,0E+0,1		1,00		
Sample 2	2	<1,0E+0,1	<1,0E+0,1	1,00	1,00	3,80
	3	<1,0E+0,1		1,00		

Bacterial strain – *Escherichia coli*

Sample	Repetition	Cell count /cm ³	Geom. mean of Cell count /cm ³	Log ₁₀ of Cell count /cm ²	Average Log ₁₀ of Cell count /cm ²	Log ₁₀ Reduction
	1	2,2E+0,4		4,35		
Ref.	2	2,3E+0,4	2,2E+0,4	4,35	4,34	
t=0h	3	2,1E+0,4		4,33		
	1	9,3E+0,4		3,97		
Ref.	2	4,4E+0,4	1,7E+0,3	2,64	3,23	

24h	3	1,2E=0,4		3,09		
	1	<1,0E+0,1		1,00		
Sample 1	2	<1,0E+0,1	<1,0E+0,1	1,00	1,00	2,23
	3	<1,0E+0,1		1,00		
	1	<1,0E+0,1		1,00		
Sample 2	2	<1,0E+0,1	<1,0E+0,1	1,00	1,00	2,23
	3	<1,0E+0,1		1,00		

Fungal strain – mould – Cladosporium cladosporioides

Sample	Repetition	Cell count /cm ³	Geom. mean of Cell count /cm ³	Log ₁₀ of Cell count /cm ²	Average Log ₁₀ of Cell count /cm ²	Log ₁₀ Reduction
	1	2,2E+0,4		4,34		
Ref.	2	2,2E+0,4	2,2E+0,4	4,35	4,34	
t=0h	3	2,2E+0,4		4,35		
	1	1,8E+0,4		3,26		
Ref.	2	1,6E+0,4	1,64E+0,3	3,21	3,22	
24h	3	1,5E=0,4		3,18		
	1	<1,0E+0,1		1,00		
Sample 1	2	<1,0E+0,1	<1,0E+0,1	1,00	1,00	2,22
	3	<1,0E+0,1		1,00		
	1	<1,0E+0,1		1,00		
Sample 2	2	<1,0E+0,1	<1,0E+0,1	1,00	1,00	2,22
	3	<1,0E+0,1		1,00		

Embodiment no. 2

A preparation containing 70% of the active ingredient according to the invention and 30% of the composition of fillers: organic filler – 17%, benzoic acid; inorganic filler – 13%, silica, is mixed with PVC material in the form of masterbatch and introduced into the material in the amount of 3% by mass.

The composition of the material and the preparation was processed through thermoforming (extrusion) at the following parameters:

Screw rotation speed: 185 rpm

Head pressure: 11-15 bar

Mass temperature: 180°C.

The obtained product is highly resistant to development of bacteria and fungi.

Embodiment no. 3

A preparation containing 85% of the active ingredient according to the invention and 15% of the composition of fillers: organic filler – 15% benzoic acid, is mixed with PP in the form of masterbatch and introduced into the material in the amount of 3% by mass.

The composition of the material and the preparation was processed through thermoforming (extrusion).

Screw rotation speed: 185 rpm

Head pressure: 12-16 bar

Mass temperature: 195°C

The obtained product is highly resistant to development of bacteria and fungi.

The test for resistance to mould fungi of PP samples with an additive of the preparation was carried out in accordance with the standard PN-EN ISO 846.

Contaminated samples were incubated at the temperature of $29\pm 1^{\circ}\text{C}$ for a period of 28 days. Relative humidity in the incubator chamber exceeded 90%.

Obtained results:

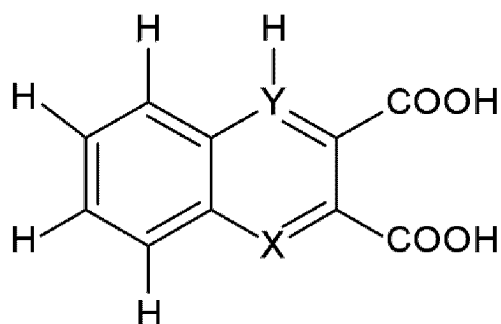
Samples	CD (+S)	CD (-S)
PP + 3% of the preparation	0	0
PP + 5% of the preparation	0	0
PP + 10% of the preparation	0	0

The results of the conducted tests of biostatic efficacy of the agent disclosed in the invention prove that a preparation containing the biologically active ingredient has a beneficial effect of bio-protective nature.

Claims

We claim:

1. An antibacterial and antifungal preparation containing, beside a biologically active ingredient used as antibacterial and antifungal ingredient, auxiliary ingredients in the form of fillers, **characterized in that** it contains a biologically active ingredient being a derivative of an acid of the formula,



where there are two carboxyl groups (-COOH), five substituents which are hydrogen (H), X signifies carbon (C) and Y signifies nitrogen (N) or X signifies nitrogen (N) and Y signifies carbon (C) in the amount of 60 to 85% by weight, and the remaining amount is a composition of inorganic and/or organic fillers.

2. Preparation according to claim 1, **characterized in that** benzoic acid, sodium benzoate and/or curcumin are used as organic fillers.
3. Preparation according to claim 1, **characterized in that** chalk and silica are used as inorganic fillers.
4. Preparation according to claim 1, **characterized in that** it is a part of a composition of plastics in the amount of 3-7% by mass.
5. Preparation according to claim 1, **characterized in that** it is a part of a composition of interior and exterior paints, varnishes and impregnations in the amount of 3-7% by mass.
6. Preparation according to claim 1, **characterized in that** it is a part of a composition of silicones and resins in the amount of 3-7% by mass.