

PATENT SPECIFICATION

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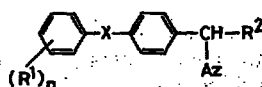
(54) AZOLYL-(1)-METHANES AND THEIR SALTS, PROCESSES
 FOR THEIR PREPARATION AND THEIR USE AS
 MEDICAMENTS

(71) We, BAYER ATKIENGESSELLSCHAFT, a body corporate organised under the laws of Germany, of Leverkusen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new azolyl-(1)-methanes and their salts, several processes for their preparation and their use as medicaments, especially as antimycotics having good antimicrobial properties.

It has already been disclosed that N-tritylimidazoles, especially bisphenyl - [2-chlorophenyl - imidazolyl - (1)] - methane (Clotrimazol, Canesten (both Registered Trade Marks) exhibit a good to very good antimycotic action [compare Belgian Patent Specification 720,801]. However, the action is not always satisfactory, especially in the case of moulds.

According to the present invention there are provided azolyl-(1)-methanes of the general formula



(I)

in which

R¹ represents halogen, halogenoalkyl, alkyl, alkoxy, nitro, benzyl or cyano,

R² represents alkyl or optionally substituted aryl,

X represents a single bond, oxygen, sulphur, the thionyl group or the sulphonyl group,

Az represents the imidazolyl-(1), pyrazolyl-(1), 1,2,4-triazolyl-(1) or 1,2,4-triazolyl-(4) radical and

n represents 0 or an integer of from 1 to 4

and salts thereof, the radicals R¹ being identical or different when n is greater than one.

The compounds of the invention (i.e. the compounds of the formula (I) and their salts) exhibit powerful antimycotic properties and at the same time an antimicrobial action. Of the compounds of the invention which are salts, those which are pharmaceutically acceptable are most important and preferred.

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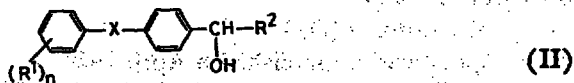
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The azolyl-(1)-methanes of the formula (I) may be obtained

(a) by reacting carbinols of the formula



in which

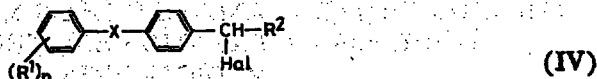
R¹, R², X and n have the abovementioned meanings with thionyl-bis-azoles of the formula



in which

Az has the abovementioned meaning, if appropriate in the presence of a diluent, or

(b) by reacting halogeno-methanes of the formula



in which

R¹, R², X and n have the abovementioned meanings and Hal represents chlorine or bromine,

1.) with azoles of the formula



in which

Az has the abovementioned meaning if appropriate in the presence of an acid-binding agent and, if appropriate, in the presence of a diluent, or

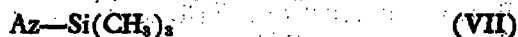
2.) with compounds of the formula



in which

Az has the abovementioned meaning and M represents silver or an alkali metal, preferably sodium or potassium, if appropriate in the presence of a diluent, or

3.) with compounds of the formula

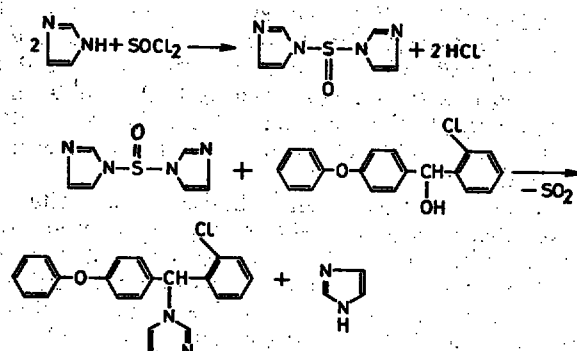


in which

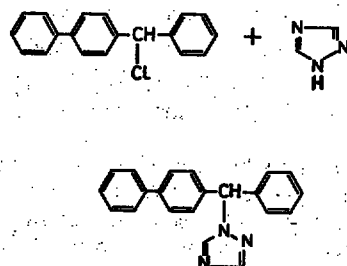
Az has the abovementioned meaning, if appropriate in the presence of a diluent.

Surprisingly, the azolyl-(1)-methanes according to the invention show, in addition to a very good and broad antimycotic action, a very powerful antibacterial activity, which is not present either in the N-tritylimidazoles known from the state of the art or in the known commercially available products, for example Nystatin, Pimaricin or Griseofulvin. The active compounds according to the invention thus represent an enrichment of pharmacy.

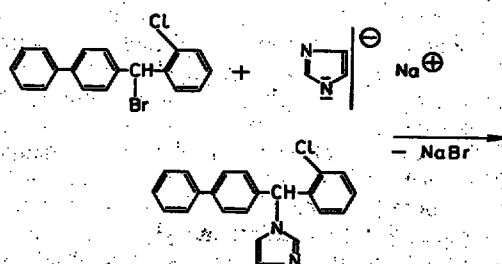
If (4 - phenoxy - phenyl) - (2 - chlorophenyl) - carbinol, thionyl chloride and imidazole are used as starting materials, the course of the reaction can be represented by the following equation (process variant (a)):



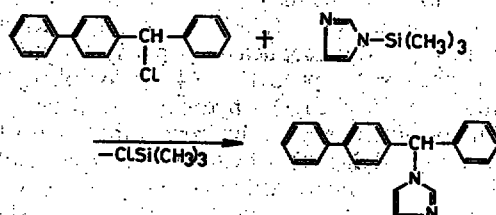
If diphenyl - phenyl - chloro - methane and 1,2,4 - triazole are used as starting materials, the course of the reaction can be represented by the following equation (process variant (b/1.)):



If diphenyl - (2 - chlorophenyl) - bromo - methane and sodium imidazole are used as starting materials, the course of the reaction can be represented by the following equation (process variant (b/2.)):



If diphenyl - phenyl - chloro - methane and trimethylsilyl - 1 - imidazole are used as starting materials, the course of the reaction can be represented by the following equation (process variant (b/3.)):



The formulae (II) and (IV) respectively provide a general definition of the carbinols and halogenomethanes used as starting materials. In these formulae, and consequently in the product of formula I, R¹ preferably represents straight-chain or branched alkyl with up to 6, in particular with up to 4, carbon atoms, examples being

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methyl, ethyl, isopropyl and tert.-butyl; alkoxy with 2 to 4, especially 2 to 3, carbon atoms, such as, for example, methoxy or ethoxy; halogen, especially fluorine, chlorine and bromine; also halogenoalkyl with up to 4 carbon atoms and up to 5 halogen atoms, especially with up to 2 carbon atoms and up to 3 identical or different halogen atoms, halogens being, in particular, fluorine and chlorine, and trifluoromethyl being mentioned as an example; and also nitro and cyano. The number n preferably represents 0 or an integer from 1 to 3.

R² preferably represents straight-chain or branched alkyl with up to 6, especially with up to 4, carbon atoms, examples being methyl, ethyl, isopropyl and tert.-butyl, or an optionally monosubstituted or polysubstituted aryl radical with 6 to 10 carbon atoms, especially with 6 carbon atoms. Preferred substituents which may be mentioned are halogen, especially fluorine, chlorine or bromine, straight-chain or branched alkyl with 1 to 6, especially 1 to 4, carbon atoms, alkoxy, alkylthio and alkylsulphonyl with 1 to 4, especially 1 to 2, carbon atoms, halogenoalkyl with 1 to 2 carbon atoms and 1 to 5 halogen atoms, especially fluorine and chlorine, the amino group and the nitro group.

The carbinols of the formula (II) which can be used according to the invention are known or can be prepared according to customary methods. They are obtained, for example, by reduction of the ketones, obtained by a Friedel-Crafts reaction, with aluminium isopropylate [compare, on this topic, Izv. Akad. SSSR, 10, 1804 (1962) and Z. obsc. Chim., 34 (3), 977 (1964)] or by a Meerwein-Ponndorf reduction [compare, on this topic, Z. org. Chim., 2 (7), 1288 (1966)]. However, the reduction can also be carried out with any other reducing agent, such as, for example, sodium borohydride.

The ketone can furthermore also be reacted with Grignard reagents [compare, on this topic, J. Pharm. Sci. 59 (7), 1042 (1970)]. A further possibility of carrying out the preparation would be the reaction of the corresponding aldehyde with Grignard compounds [compare, on this topic, J. Pharm. Sci., 62 (6), 952 (1973), and J. Org. Chem. 36 (18), 2724 (1971)].

The following may be mentioned as examples of the carbinols of the formula (II) which can be used according to the invention: (4 - phenoxy - phenyl) - (2-chlorophenyl) - hydroxy - methane, diphenyl - phenyl - hydroxy - methane, [4 - (4' - chlorophenyl) - phenyl] - (4 - ethylphenyl) - hydroxy - methane, [4 - (2'-methylphenyl - thio) - phenyl] - (3 - methoxyphenyl) - hydroxy - methane, [4 - (4'-bromophenylthio) - phenyl] - (4 - trifluoromethylphenyl) - hydroxy - methane, [4 - (2' - methyl - 4' - chlorophenylsulphonyl) - phenyl] - (3 - bromophenyl) - hydroxy - methane, [4 - (4' - methoxyphenoxy) - phenyl] - tert. - butyl - hydroxy - methane, [4 - (4' - trifluoromethylphenyl) - phenyl] - tert. - butyl - hydroxy - methane, [4 - (2',4',6' - trichlorophenylthio) - phenyl] - (4 - tert. - butylphenyl) - hydroxy - methane, [4 - (2',6' - dichlorophenoxy) - phenyl] - phenyl - hydroxy - methane, [4 - (2',6' - dichlorophenoxy) - phenyl] - tert. - butyl - hydroxy - methane, [4 - (2',4',6' - trichlorophenoxy) - phenyl] - phenyl - hydroxy - methane, [4 - (4'-chlorophenylthio) - phenyl] - (4 - chlorophenyl) - hydroxy - methane, (4 - phenylthio - phenyl) - phenyl - hydroxy - methane, (4 - phenylsulphonyl - phenyl) - phenyl - hydroxy - methane, diphenyl - (3 - methylphenyl) - hydroxy - methane, diphenyl - (3,5 - dimethylphenyl) - hydroxy - methane, diphenyl - (4 - chlorophenyl) - hydroxy - methane, diphenyl - (2,4 - dichlorophenyl) - hydroxy - methane, diphenyl - (4 - bromophenyl) - hydroxy - methane, diphenyl - (4 - fluorophenyl) - hydroxy - methane, diphenyl - (4 - trifluoromethylphenyl) - hydroxy - methane, diphenyl - (4 - methylsulphonylphenyl) - hydroxy - methane, [4 - (2',4' - dichlorophenyl) - phenyl] - phenyl - hydroxy - methane, [4 - (2',4',6' - trichlorophenyl) - phenyl] - phenyl - hydroxy - methane, [4 - (4' - bromophenyl) - phenyl] - phenyl - hydroxy - methane, [4 - (2',6' - dichlorophenoxy) - phenyl] - (4 - chlorophenyl) - hydroxy - methane, diphenyl - (3 - trifluoromethylphenyl) - hydroxy - methane, [4 - (4' - chlorophenyl) - phenyl] - (3 - trifluoromethylphenyl) - hydroxy - methane, [4 - (4' - bromophenyl) - phenyl] - 3 - trifluoromethylphenyl - hydroxy - methane and [4 - (2',6' - dichlorophenoxy) - phenyl] - (3 - trifluoromethylphenyl) - hydroxy - methane.

The halogeno-methanes of the formula (IV) which can be used according to the invention are known or can be prepared according to customary methods. They are obtained, *inter alia*, by halogenation of the carbinols of the formula (II), for example with hydrogen chloride [compare, on this topic, J. Org. Chem. 36 (18), 2724 (1971)] or with thionyl chloride [compare, on this topic, Izv. Akad. SSSR, 10, 1804 (1962)]. The following may be mentioned as examples of the halogeno-

methanes of the formula (IV) which can be used according to the invention: (4-phenoxy - phenyl) - (2 - chlorophenyl) - chloro - methane, diphenyl - phenyl-chloro - methane, [4 - (4' - chlorophenyl) - phenyl] - (4 - ethylphenyl) - chloro-methane, [4 - (2' - methylphenylthio) - phenyl] - (3 - methoxyphenyl) - chloro-methane, [4 - (4' - bromophenylthio) - phenyl] - (4 - trifluoromethylphenyl) - bromo - methane, [4 - (2' - methyl - 4' - chlorophenylsulphonyl) - phenyl] - (3-bromophenyl) - bromo - methane, [4 - (4' - methoxyphenoxy) - phenyl] - tert-butyl - bromo - methane, [4 - (4' - trifluoromethylphenyl) - phenyl] - tert - butyl-bromo - methane, [4 - (2',4',6' - trichlorophenylthio) - phenyl] - (4 - tert - butylphenyl) - chloro - methane, [4 - (2',6' - dichlorophenoxy) - phenyl] - phenyl-chloro - methane, [4 - (2',6' - dichlorophenoxy) - phenyl] - tert - butyl - chloro-methane, [4 - (2',4',6' - trichlorophenoxy) - phenyl] - phenyl - chloro - methane, [4 - (4' - chlorophenylthio) - phenyl] - (4 - chlorophenyl) - bromo - methane, (4-phenylthio - phenyl) - phenyl - bromo - methane, (4 - phenyl - sulphonylphenyl) - phenyl - bromo - methane, diphenyl - (3 - methylphenyl) - bromo - methane, diphenyl - (3,5 - dimethylphenyl) - chloro - methane, diphenyl - (4 - chlorophenyl) - chloro - methane, diphenyl - (2,4 - dichlorophenyl) - chloro - methane, diphenyl - (4 - bromophenyl) - chloro - methane, diphenyl - (4 - fluorophenyl) - bromo-methane, diphenyl - (4 - trifluoromethylphenyl) - bromo - methane, diphenyl - (4-methyl - sulphonylphenyl) - bromo - methane, [4 - (2',4' - dichlorophenyl) - phenyl] - phenyl - bromo - methane, [4 - (2',4',6' - trichlorophenyl) - phenyl] - phenyl-chloro - methane, [4 - (4' - bromophenyl) - phenyl] - phenyl - chloro - methane, [4 - (2',6' - dichlorophenoxy) - phenyl] - (4 - chlorophenyl) - chloro - methane, diphenyl - (3 - trifluoromethylphenyl) - chloro - methane, [4 - (4' - chlorophenyl) - phenyl] - (3 - trifluoromethylphenyl) - bromo - methane, [4 - (4' - bromophenyl) - phenyl] - (3 - trifluoromethylphenyl) - bromo - methane and [4 - (2',6' - dichlorophenoxy) - phenyl] - (3 - trifluoromethylphenyl) - bromo - methane.

Pharmaceutically acceptable salts of the compounds of the formula (I) are the salts of physiologically tolerable acids. These preferentially include the hydrogen halide acids, such as, for example, hydrochloric acid and hydrobromic acid, especially hydrochloric acid, and phosphoric acid, nitric acid, monofunctional and bifunctional carboxylic acids and hydroxycarboxylic acids, such as, for example, acetic acid, maleic acid, succinic acid, fumaric acid, tartaric acid, citric acid, salicylic acid, sorbic acid and lactic acid, and 1,5-naphthalene-disulphonic acid.

Diluents which can be used for the reaction according to the invention, in accordance with process variant (a), are preferably polar organic solvents. These preferentially include nitriles, such as acetonitrile; sulphoxides, such as dimethylsulphoxide; formamides, such as dimethylformamide; ketones, such as acetone; ethers, such as diethyl ether and tetrahydrofuran, and especially chlorohydrocarbons, such as methylene chloride and chloroform.

In process (a), the reaction temperatures can be varied within a substantial range. In general, the reaction is carried out at between 0 and 120°C, preferably at 10 to 85°C. In the presence of a solvent, the reaction is preferably carried out at the boiling point of the particular solvent.

In carrying out the process (a) according to the invention, preferably about 2 mols of thionyl-bis-azole of the formula (III) are employed per mol of the compound of the formula (II), or thionyl-bis-azole is produced *in situ*.

To isolate the compound of the formula (I), the solvent is distilled off, the residue is taken up in an organic solvent and the solution is washed with water. The organic phase is dried over sodium sulphate and freed from the solvent in vacuo. The residue is purified by recrystallisation or salt formation.

For the reaction according to the invention, in accordance with process variant (b/1.), inert organic solvents can be used as diluents. These preferentially include ketones, such as diethyl ketone and especially acetone and methyl ethyl ketone; nitriles, such as propionitrile and especially acetonitrile; alcohols, such as ethanol or isopropanol; ethers, such as tetrahydrofuran or dioxane; benzene, formamides, such as, in particular, dimethylformamide; halogenated hydrocarbons and hexamethylphosphoric acid triamide.

The reaction according to process (b/1.) is preferably carried out in the presence of an acid-binding agent. It is possible to add any inorganic or organic acid-binding agents which can usually be employed, such as alkali metal carbonates, for example sodium carbonate, potassium carbonate and sodium bicarbonate, or lower tertiary alkylamines, cycloalkylamines or arylamines, for example triethylamine and di-

methylaniline, or pyridine and diazabicyclooctane. Furthermore, an excess of azole can be used.

The reaction temperatures in process (b/1.) can be varied within a substantial range. In general, the reaction is carried out between 20 and 150°C, preferably at 80 to 120°C. In the presence of a solvent, the reaction is preferably carried out at the boiling point of the particular solvent.

In carrying out process (b/1.) according to the invention, preferably about 1 mol of the azole of the formula (V) and about 1 mol of acid-binding agent are employed per mol of the compound of the formula (IV).

To isolate the compounds of the formula (I), the solvent is distilled off, the residue is taken up in an organic solvent and the solution is washed with water. The organic phase is dried over sodium sulphate and freed from the solvent in vacuo. The residue is purified by distillation or recrystallisation.

For the reaction according to the invention, in accordance with process variants (b/2. and b/3.), inert organic solvents can be used as diluents. The preferred solvents are those already mentioned in connection with process variant (b/1.).

In process variants (b/2. and b/3.) the reaction temperatures can be varied within a substantial range. In general, the reaction is carried out between -10 and 100°C, preferably at 0 to 85°C.

In carrying out the process of the invention according to variants (b/2. and b/3.), the reactants of the formulae (IV) and (VI) or (VII) are employed in approximately equimolar amounts. The reaction products obtained are isolated and purified in the customary manner, which has already been described in connection with process variant (b/1.).

The salts of the compounds of the formula (I) can be obtained in a simple manner, in accordance with customary methods of forming salts, for example by dissolving the base in ether, for example diethyl ether, and adding the acid, for example hydrogen chloride, and can be isolated in a known manner, for example by filtering off, and can be purified if desired.

The new compounds of the formula (I) and their salts exhibit very powerful antimycotic effects. They show a broad spectrum of action *in vitro*, which encompasses dermatophytes, yeasts, *Pityrosporum ovale*, moulds and biphasic fungi. They can, therefore, be employed with good success against fungal infections in man and animals.

The following may be mentioned as examples of fields of application in human medicine; dermatomycoses and systemic mycoses caused by *Trichophyton mentagrophytes* and other species of *Trichophyton*, species of *Microsporon*, *Epidermophyton floccosum*, blastomycoses and biphasic fungi as well as moulds.

The following may be mentioned as examples of fields of application in veterinary medicine: all dermatomycoses and systemic mycoses, especially those caused by the abovementioned pathogens.

Furthermore, the active compounds according to the invention, whilst having a low toxicity and good toleration, exhibit a strong antibacterial activity. These properties permit their use as active compounds, not only in medicine, but also for preserving inorganic and organic materials, especially organic materials of all kinds, for example polymers, lubricants, dyestuffs, fibres, leather, paper and timber, foodstuffs, cosmetics, such as creams and ointments, and water.

The active compounds according to the invention are active against a very broad spectrum of micro-organisms. By using them, it is possible to combat, for example, gram-negative and gram-positive bacteria and bacteria-like micro-organisms and to prevent, ameliorate and/or cure the illnesses caused by these pathogens.

The active compounds according to the invention are particularly active against bacteria and bacteria-like micro-organisms. They are therefore particularly suitable for the prophylaxis and chemotherapy of local and systemic infections in human medicine and veterinary medicine, caused by these pathogens.

For example, it is possible to treat and/or prevent local and/or systemic illnesses caused by the following pathogens or by mixtures of the following pathogens:

Micrococcaceae, such as *Staphylococci*, for example *Staphylococcus aureus*, *Staph. epidermidis*, *Staph. aerogenes* and *Gaffkya tetragena* (*Staph.* = *Staphylococcus*);

Lactobacteriaceae, such as *Streptococci*, for example *Streptococcus pyogenes*, α - and β -haemolysing *Streptococci*, non-(γ)-haemolysing *Streptococci*, *Str. viridans*, *Str. faecalis* (*Enterococci*), *Str. agalactiae*, *Str. lactis*, *Str. equi*, *Str. anaerobis* and

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Diplococcus pneumoniae (Pneumococci) (Str. = Streptococcus);

Neisseriaceae, such as Neisseriae, for example Neisseria gonorrhoeae (Gonococci), N. meningitidis (Meningococci), N. catarrhalis and N. flava (N. = Neisseria);

Corynebacteriaceae, such as Corynebacteria, for example Corynebacterium diphtheriae, C. pyogenes, C. diphtheroides, C. acnes, C. parvum, C. bovis, C. renale, C. ovis and C. murisepticum, Listeria bacteria, for example Listeria monocytogenes, Erysipelothrix bacteria, for example Erysipelothrix insidiosa and Kurthia bacteria, for example Kurthia zopfii (C. = Corynebacterium);

Enterobacteriaceae, such as Escherichiae bacteria of the coli group: Escherichia bacteria, for example Escherichia coli, Aerobacter bacteria, for example A. aerogenes and A. cloacae, Klebsiella bacteria, for example K. pneumoniae and K. ozaenae, Erwiniae, for example Erwinia spec., Serratia, for example Serratia marcescens (A. = Aerobacter) (K. = Klebsiella), Proteae bacteria of the Proteus group: Proteus, for example Proteus vulgaris, Pr. morganii, Pr. rettgeri and Pr. mirabilis, and Providencia, for example Providencia sp. (Pr. = Proteus), Salmonelleae: Salmonella bacteria, for example Salmonella paratyphi A and B, S. typhi, S. enteritidis, S. cholerae suis and S. typhimurium (S. = Salmonella), Shigella bacteria, for example Shigella dysenteriae, Sh. ambigua, Sh. flexneri, Sh. boydii and Sh. sonnei (Sh. = Shigella); Pseudomonadeaceae, such as Pseudomonas bacteria, for example Pseudomonas aeruginosa and Ps. pseudomallei (Ps. = Pseudomonas) and Aeromonas bacteria, for example Aeromonas liquefaciens and A. hydrophila (A. = Aeromonas);

Parvobacteriaceae or Brucellaceae, such as Pasteurella bacteria, for example Pasteurella multocida, Past. pestis (Yersinia), Past. pseudotuberculosis and Past. tularensis (Past. = Pasteurella), Brucella bacteria, for example Brucella abortus, Br. melitensis and Br. suis (Br. = Brucella), Haemophilus bacteria, for example Haemophilus influenzae, H. ducreyi, H. suis, H. canis and H. aegypticus (H. = Haemophilus), Bordetella bacteria, for example Bordetella pertussis and B. bronchiseptica (B. = Bordetella) and Moraxella bacteria, for example Moraxella lacunata.

The above list of pathogens is purely by way of example and is in no way to be interpreted as imposing a limit.

The following may be mentioned as example of illnesses which can be prevented, ameliorated and/or cured by the active compounds according to the invention: illnesses of the respiratory tracts and of the pharyngeal cavity; otitis; pharyngitis; pneumonia; peritonitis; pyelonephritis; cystitis; endocarditis; systemic infections; bronchitis; arthritis and other systemic infections, as well as local infections, for example of the skin and of locally accessible mucous membranes.

The present invention provides a pharmaceutical composition containing as active ingredient a compound of the invention in admixture with a solid or liquefied gaseous diluent, or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 (preferably less than 350) and a surface active agent.

The invention further provides a pharmaceutical composition containing as active ingredient a compound of the invention, which composition is in the form of a sterile or isotonic aqueous solution.

The invention also provides a medicament in dosage unit form comprising a compound of the invention either alone or in admixture with a diluent.

The invention also provides a medicament in the form of tablets (including lozenges and granules), dragees, capsules, pills, ampoules or suppositories comprising a compound of the invention either alone or in admixture with the diluent.

"Medicament" as used in this Specification means physically discrete coherent portions suitable for medical administration. "Medicament in dosage unit form" as used in this Specification means physically discrete coherent portions suitable for medical administration each containing a daily dose or a multiple (up to four times) or sub-multiple (down to a fortieth) of a daily dose of the compound of the invention. Whether the medicament contains a daily dose or, for example, a half, a third, or a quarter of a daily dose will depend on whether the medicament is to be administered once or, for example, twice, three times or four times a day respectively.

The pharmaceutical compositions according to the invention, may, for example, take the form of ointments, gels, pastes, creams, sprays (including aerosols), lotions, suspensions, solutions and emulsions of the active ingredients in aqueous or non-aqueous diluents, sprays, granules or powders.

The diluents to be used in pharmaceutical compositions (e.g. granulates) adapted to be formed into tablets, dragees, capsules and pills include the following:

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(a) fillers and extenders, e.g. starch, sugars, mannitol, and silicic acid; (b) binding agents, e.g. carboxymethyl cellulose and other cellulose derivatives, alginates, gelatine and polyvinyl pyrrolidone; (c) moisturizing agents, e.g. glycerol; (d) disintegrating agents, e.g. agar-agar, calcium carbonate and sodium bicarbonate; (e) agents for detarding dissolution e.g. paraffin; (f) resorption accelerators, e.g. quaternary ammonium compounds; (g) surface active agents, e.g. cetyl alcohol, glycerol monostearate; (h) adsorptive carriers, e.g. kaolin and bentonite; (i) lubricants, e.g. talc, calcium and magnesium stearate and solid polyethylene glycols.

The tablets, dragees, capsules and pills formed from the pharmaceutical compositions of the invention can have the customary coatings, envelopes and protective matrices, which may contain opacifiers. They can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes and protective matrices may be made, for example, of polymeric substances or waxes.

The ingredient can also be made up in microencapsulated form together with one or several of the above-mentioned diluents.

The diluents to be used in pharmaceutical compositions adapted to be formed into suppositories can, for example, be the usual water-soluble or water-insoluble diluents, such as polyethylene glycols and fats (e.g. cocoa oil and high esters [e.g. C₁₄-alcohol with C₁₈-fatty acid]) or mixtures of these diluents.

The pharmaceutical compositions which are ointments, pastes, creams and gels can, for example, contain the usual diluents, e.g. animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures of these substances.

The pharmaceutical compositions which are powders and sprays can, for example, contain the usual diluents, e.g. lactose, talc, silicic acid, aluminium hydroxide, calcium silicate, and polyamide powder or mixtures of these substances. Aerosol sprays can, for example, contain the usual propellants, e.g. chlorofluorohydrocarbons.

The pharmaceutical compositions which are solutions and emulsions can, for example, contain the customary diluents (with, of course, the above-mentioned exclusion of solvents having a molecular weight below 200 except in the presence of a surface-active agent), such as solvents, dissolving agents and emulsifiers; specific examples of such diluents are water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils [for example ground nut oil], glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitol or mixtures thereof.

For parenteral administration, the solutions and emulsions should be sterile, and, if appropriate, block-isotonic.

The pharmaceutical compositions which are suspensions can contain the usual diluents, such as liquid diluents, e.g. water, ethyl alcohol, propylene glycol, surface-active agents (e.g. ethoxylated isostearyl alcohols, polyoxyethylene sorbite and sorbitane esters), microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixtures thereof.

All the pharmaceutical compositions according to the invention can also contain colouring agents and preservatives as well as perfumes and flavouring additions e.g. peppermint oil and eucalyptus oil) and sweetening agents (e.g. saccharin).

The pharmaceutical compositions according to the invention preferably contain 0.1 to 99.5, more preferably from 4.5 to 95% of the active ingredient by weight of the total composition.

In addition to a compound of the invention, the pharmaceutical compositions and medicaments according to the invention can also contain other pharmaceutically active compounds. They may also contain a plurality of compounds of the invention.

Any diluent in the medicaments of the present invention may be any of those mentioned above in relation to the pharmaceutical compositions of the present invention. Such medicaments may include solvents of molecular weight less than 200 as sole diluent.

The discrete coherent portions constituting the medicament according to the invention (whether in dosage unit form or not), may be, for example, any of the following: tablets (including lozenges and granules), pills, dragees, capsules, suppositories and ampoules. Some of these forms may be made up for delayed release of the active ingredient. Some, such as capsules, include a protective envelope which renders the portions of the medicament physically discrete and coherent.

The preferred daily dose for administration of the medicaments of the invention is 400 mg to 50 g of active ingredient.

The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

This invention further provides a method of combating (including prevention, relief and cure of) the above-mentioned diseases in human and non-human animals, which comprises administering to the animals a compound of the invention alone or in admixture with a diluent or in the form of a medicament according to the invention.

It is envisaged that these active compounds will be administered perorally, parenterally (for example intramuscularly, intraperitoneally or intravenously), rectally or locally, preferably orally or locally when they are used as antimycotic agents, and are preferably administered parenterally, especially intravenously and intramuscularly, when used as antimicrobial agents. Preferred pharmaceutical compositions and medicaments are therefore those adapted for oral, local or parenteral administration.

In general it has proved advantageous both in human medicine and in veterinary medicine, to administer the active compound or compounds according to the invention in total amounts of about 8 to about 500, preferably 30 to 250, mg/kg of body weight every 24 hours, optionally in the form of several individual administrations, to achieve the desired results.

It can, however, be necessary to deviate from the dosages mentioned and in particular to do so as a function of the type and body weight of the subject to be treated, the nature and severity of the illness, the nature of the preparation and the administration of the medicine, and the time or interval during which administration takes place. Thus it can in some cases suffice to manage with less than the above-mentioned amount of active compound whilst in other cases the abovementioned amount of active compound must be exceeded. Any expert can easily decide the particular requisite optimum dosage and method of administration of the active compounds on the basis of his expert knowledge.

When used as a feedstuff additive, the new compounds can be administered in the usual manner together with the feedstuff or with feedstuff preparations, or with the drinking water. In this way, an infection by gram-negative or gram-positive bacteria can be prevented and, equally, better utilisation of the feedstuff can be achieved.

The good antimycotic activity and the powerful antibacterial effects coupled with oral resorbability can be demonstrated, by way of example, by the following *in vitro* experiments (compare Examples A and B).

According to these data, the preparations claimed have, as regards their antimycotic properties, not only a broad spectrum of action but also a pronounced action peak against moulds and *Pityrosporum ovale*. Particularly in the case of moulds, the MIC values are, for a comparable test method, better by a factor of 10 than for

Clotrimazol and better by up to a factor of 100 than for Nystatin, Pimaricin and Amphotericin B, as well as Griseofulvin.

As regards their antibacterial effects, the products also prove superior to Clotrimazol and other known azole derivatives as well as to the abovementioned commercially available products, since the new preparations are additionally active against gram-negative bacteria.

A.) Antimycotic activity *in vitro*

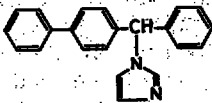
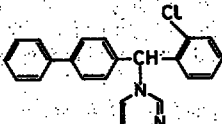
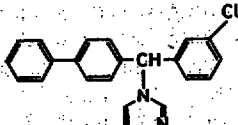
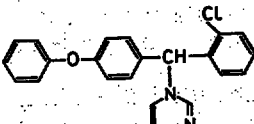
The MIC values of some compounds against important classes of fungi are listed in the table which follows.

The *in vitro* tests were carried out in a series dilution test with germ inocula averaging 5×10^4 germs/ml of substrate. The nutrient media used were

- for dermatophytes and moulds: Sabouraud's milieu d'épreuve,
- for yeasts: meat extract-glucose bouillon,
- for *Pityrosporum ovale*: Abbe medium, and
- for biphasic fungi in the yeast phase: Francis's blood agar.

The incubation temperatures were 28°C for dermatophytes, yeasts and moulds and 37°C for biphasic fungi; the incubation time was 24—96 hours.

TABLE A: Antimycotic activity *in vitro*

Active compound	MIC values in μ /ml of nutrient medium, for					
	Trichophyton mentagrophytes	Candida albicans	Pityrosporum ovale	Aspergillus fumigatus	Penicillium	Histoplasma
	<1	4	1	<0.1	<0.1	4
	<1	2	1	<0.1	<0.1	4
	2	1	1	<0.1	<0.1	2
	16	8	1	<0.1	<0.1	2

B.) Antibacterial activity *in vitro*

The *in vitro* tests were carried out by the plate test. In this, the bacteria were cast with the agar, at a concentration of 5×10^8 /plate. The concentration in the plate which showed no formation of colonies is the MIC. The nutrient medium has the following composition:

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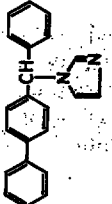
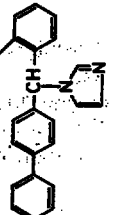
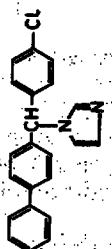
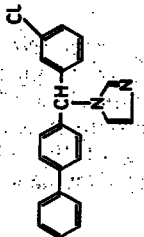
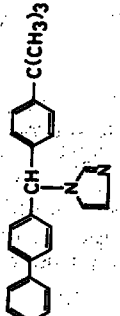
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Proteose peptone	10 g
Veal extract	10 g
Dextrose	2 g
NaCl	3 g
Disodium phosphate	2 g
Na acetate	1 g
Adenine sulphate	0.01 g
Guanine hydrochloride	0.01 g
Uracil	0.01 g
Xanthine	0.01 g
Agar	12.0 g
pH 7.4	1,000 ml distilled water

23

TABLE B: Antibacterial activity in vitro

Active compound	Streptococcus pyogenes W	MIC values for		Pseudomonas aerug. B	Proteus vul- garis 1017	Klebsiella 8085
		Staphylococcus aureus 133	E - coli A 261			
	10-20	8	-	-	128	128
	128	8	256	256	128	128
	10	8	-	-	-	-
	128	8	-	-	-	-
	128	8	-	256	128	128

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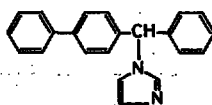
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Preparation examples

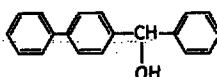
Example 1.



Process variant (a)

13.6 g (0.2 mol) of imidazole are dissolved in 150 ml of acetonitrile and 3.5 ml of thionyl chloride are added at 10°C. 13 g (0.05 mol) of diphenyl-phenyl-carbinol are added to the solution of thionyl-bis imidazole thus obtained. After standing for 15 hours at room temperature, the solvent is removed by distilling off in vacuo. The residue is taken up in chloroform and the solution is washed with water. The organic phase is separated off, dried over sodium sulphate and filtered and the solvent is distilled off in vacuo. The oily residue is dissolved in ethyl acetate and freed from insoluble, resinous constituents by filtration. The solvent is again distilled off in vacuo and the residue is purified by recrystallisation from acetonitrile. 8.7 g (56% of theory) of diphenyl-imidazolyl(1)-phenyl-methane of melting point 142°C are obtained.

Starting material

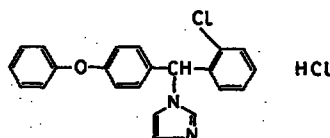


38.8 g (0.15 mol) of 4-phenyl-benzophenone are dissolved in 200 ml of ethanol and 3 g (0.075 mol) of sodium borohydride are added. After heating for 15 hours under reflux, and allowing to cool, the reaction mixture is hydrolysed with water containing a little hydrochloric acid. The solid thereby produced is purified by recrystallisation from ethanol. 36 g (89% of theory) of diphenyl-phenyl-carbinol of melting point 72—73°C are obtained.

Process variant (b/3.)

167 g (0.6 mol) of diphenyl-phenyl-chloro-methane and 92 g (0.66 mol) of trimethylsilylimidazole, dissolved in 500 ml of acetonitrile, are heated under reflux for 15 hours. After distilling off the solvent, the crystalline residue is purified by recrystallisation from ethyl acetate. 97 g (52% of theory) of diphenyl-imidazole-(1)-phenyl-methane of melting point 142°C are obtained.

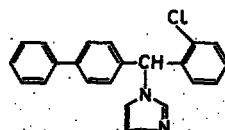
Example 2.



Process variant (b/1.), with salt formation

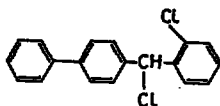
32.9 g (0.1 mol) of (4-phenoxy-phenyl)-(2-chlorophenyl)-chloro-methane and 6.8 g (0.1 mol) of imidazole are heated for 2 hours to 120°C, whilst stirring. After having cooled, the glassy mass is dissolved in acetone and the solution is stirred with diisopropyl ether. 40 g (100% of theory) of 2-chlorophenyl-imidazolyl-(1)-(4-phenoxy-phenyl)-methane hydrochloride of melting point 150°C are obtained.

Example 3.



Process variant (b/2.)

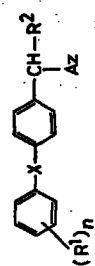
A solution of 13.6 g (0.2 mol) of imidazole in 100 ml of acetonitrile is added dropwise to a suspension of 10.8 g (0.13 mol) of sodium methylate in 200 ml of acetonitrile. The resulting sodium imidazole is filtered off and suspended in 300 ml of acetonitrile, and 31.3 g (0.1 mol) of 2-chlorophenyl-diphenyl-chloro-methane are added. After heating for 24 hours to 80°C, the mixture is allowed to cool, and is filtered. The filtrate is freed from the solvent by distilling the latter off in vacuo. The oil which remains is dissolved in ethyl acetate and the solution is washed with water, dried over sodium sulphate, filtered and freed from the solvent in vacuo. The oily residue is dissolved in chloroform and chromatographed on a silica gel column. After separating off a chloroform fraction containing a compound of melting point 150°C, the chloroform fraction containing the desired end product is obtained. After distilling off the solvent, 10.7 g (31% of theory) of 2 - chlorophenyl - imidazolyl-(1) - diphenyl - methane of melting point 90°C are obtained.

Starting material

290 g (0.985 mol) of 2-chlorophenyl-diphenyl-carbinol are dissolved in 1,000 ml of benzene and a solution of 144 ml (2 mols) of thionyl chloride in 400 ml of benzene is added slowly at 40°C, whilst stirring. The reaction mixture is heated under reflux for 15 hours. The solvent is distilled off in vacuo and the residue is stirred with 500 ml of petroleum ether. The crystals produced are filtered off and purified by recrystallisation from ethanol. 36 g (89% of theory) of 2-chlorophenyl-diphenyl-chloro-methane of melting point 80°C are obtained.

The compounds of Table 1 which follows are obtained analogously to Examples 1 to 3.

TABLE I



Example No.	R ¹	X	R ²	Az	Melting point (°C)
4	H	—		Imidazolyl- (1)	Oil
5	H	—		"	Oil
6	H	—		"	200
7	H	—		"	Oil
8	4-Cl	—		"	114
9	4-Cl	—		"	130

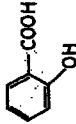
TABLE 1 (continuation)

Example No.	R ¹	X	R ²	Az	Melting point (°C)
10	H	-O-		ImidazolyI- (1)	Oil
11	H	-		"	150 (x CH ₃ COOH)
12	H	-		"	186 (x HNO ₃)
13	H	-		"	130 (x H ₂ SO ₄)
14	H	-		"	220 (x HCl)
15	H	-		"	190 (x H ₃ PO ₄)
16	H	-		"	135 (x $\text{CH}_3\text{-CH}(\text{OH})\text{-COOH}$)

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TABLE 1 (continuation)

Example No.	R ¹	X	R ²	Az	Melting point (°C)
17	H	-		Imidazolyl- (1)	Oil (x )
18	H	-S-		"	72°C
19	H	-	-C(CH ₃) ₃	"	
20	H	-		"	
21	H	-O-	-C(CH ₃) ₃	"	
22	2,4,6-Cl ₃	-		"	
23	3-C ₂ H ₅	-		"	
24	4-Cl	-	-C ₂ H ₅ -n	"	
25	H	-SO ₂ -		"	

28

TABLE 1 (continuation)

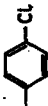
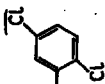
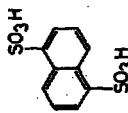
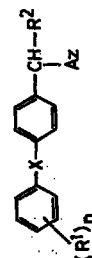
Example No.	R ¹	X	R ²	Az	Melting point (°C)
26		—		Imidazolyl- (1)	
27	H	—O—		"	Oil
28	H	—		"	
29	H	—		Pyrazolyl- (1)	90
30	H	—		"	
31	H	—O—		"	
32	H	—		1,2,4-Triazolyl- (1)	169
33	3-CH ₃	—		"	

TABLE 1 (continuation)

Example No.	R ¹	X	R ²	Az	Melting point (°C)
34	H	—		1,2,4-Triazolyl- (1)	
35	4-Cl	—		1,2,4-Triazolyl- (4)	
36	H	—		Imidazolyl- (1)	260 (× ½ )

WHAT WE CLAIM IS:—

1. An azolyl-(1)-methane of the general formula



in which

R¹ represents halogen, halogenoalkyl, alkyl, alkoxy, nitro, benzyl or cyano,
R² represents alkyl or optionally substituted aryl,

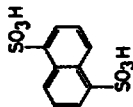
X represents a single bond, oxygen, sulphur, a thionyl group or a sulphonyl group,

Az represents an imidazolyl-(1), pyrazolyl-(1), 1,2,4-triazolyl-(1) or 1,2,4-triazolyl-(4) group and

n represents 0 or an integer of from 1 to 4
or a salt thereof, the radicals R' being identical or different when n is greater than one.

TABLE I (continuation)

Example No.	R ¹	X	R ²	Az	Melting point (°C)
34	H	—		1,2,4-Triazolyl- (1)	
35	4-Cl	—		1,2,4-Triazolyl- (4)	
36	H	—		Imidazolyl- (1)	260 (× ½)



WHAT WE CLAIM IS:—

1. An azolyl-(1)-methane of the general formula



in which

R¹ represents halogen, halogenoalkyl, alkyl, alkoxy, nitro, benzyl or cyano,R² represents alkyl or optionally substituted aryl,

X represents a single bond, oxygen, sulphur, a thionyl group or a sulphonyl group,

Az represents an imidazolyl-(1), pyrazolyl-(1), 1,2,4-triazolyl-(1) or 1,2,4-triazolyl-(4) group and

n represents 0 or an integer of from 1 to 4

or a salt thereof, the radicals R' being identical or different when n is greater than one.

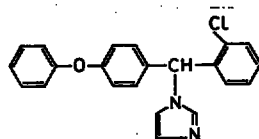


2. A compound according to claim 1 wherein

R¹ represents a straight-chain or branched alkyl group of from 1 to 6 carbon atoms, an alkoxy group of from 2 to 4 carbon atoms, a fluorine, chlorine or bromine atom, a halogenoalkyl group of from 1 to 4 carbon atoms and from 1 to 5 halogen atoms, a nitro group or a cyano group;

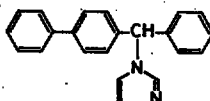
R² represents a straight-chain or branched alkyl group of from 1 to 6 carbon atoms, or an aryl group of from 6 to 10 carbon atoms optionally substituted by one or more halogen atoms, alkyl groups of from 1 to 6 carbon atoms, alkoxy, alkylthio and alkylsulphonyl groups of from 1 to 4 carbon atoms, halogenoalkyl groups of 1 or 2 carbon atoms and from 1 to 5 halogen atoms, and amine and nitro groups; and n is 0 or an integer of from 1 to 3.

3. A compound of the formula



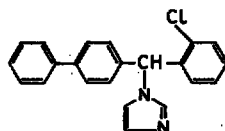
or a salt thereof.

4. A compound of the formula



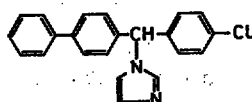
or a salt thereof.

5. A compound of the formula



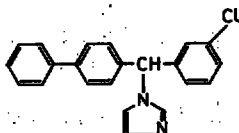
or a salt thereof.

6. A compound of the formula



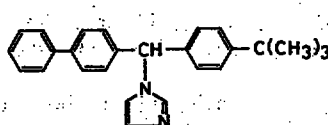
or a salt thereof.

7. A compound of the formula



or a salt thereof.

8. A compound of the formula



or a salt thereof.

9. A compound according to any one of claims 1 to 8 in the form of a salt of a hydrogen halide acid, phosphoric acid, nitric acid, or a mono- or bifunctional carboxylic or hydroxycarboxylic acid.



(32)

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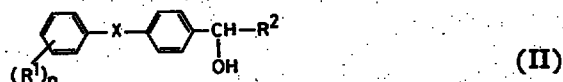
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10. Any compound of the formula (I) specifically mentioned herein other than the compound described in Example 36.

11. A process for the preparation of a compound of the formula (I) or a salt thereof comprising either

5 (a) reacting a carbinol of the formula



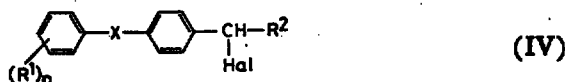
in which R¹, R², X and n are as defined in claim 1 with a thionyl-bis-azole of the formula



10 in which

Az is as defined in claim 1, or

(b) reacting a halogeno-methane of the formula



15

in which R¹, R², X and n are as defined in claim 1 and Hal represents chlorine or bromine,

15

1.) with an azole of the formula



in which Az is as defined in claim 1 if appropriate in the presence of an acid-binding agent, or

20 2.) with a compound of the formula



20

in which Az is as defined in claim 1 and M represents silver or an alkali metal, or

3.) with a compound of the formula

25



25

in which Az has the meaning defined in claim 1 and the azolyl-(1)-methanes thereby obtained are reacted, if desired, with an acid to form a salt.

30

12. A process according to claim 11 wherein the reaction is carried out in the presence of a diluent.

30

13. A process according to claim 11 or claim 12 wherein the reaction of the compounds of the formulae (II) and (III) is effected at a temperature of from 0 to 120°C.

35

14. A process according to claim 11 or claim 12 wherein the reaction of the compounds of the formulae (IV) and (V) is effected at a temperature of from 20 to 150°C.

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15. A process according to claim 11 or claim 12 wherein the reaction of the compounds of the formulae (IV) and (VI) or the reaction of the compounds of the formulae (IV) and (VII) is effected at a temperature of from -10 to +100°C.

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16. A process for preparation of a compound according to claim 1 substantially as hereinbefore described in any one of Examples 1 to 35.

40

17. A compound according to claim 1 prepared by a process according to any one of claims 11 to 16.



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- 5 18. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 10 and 17 in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 except in the presence of a surface-active agent.
- 5 19. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 10 and 17, which composition is in the form of a sterile or isotonic aqueous solution.
- 10 20. A composition according to claim 18 or 19 containing from 0.5 to 95% by weight of the said active ingredient.
- 10 21. A medicament in dosage unit form comprising a compound according to any one of claims 1 to 10 and 17 either alone or in admixture with a diluent.
- 15 22. A medicament in the form of tablets, pills, dragees, capsules, ampoules, or suppositories comprising a compound according to any one of claims 1 to 10 and 17, either alone or in admixture with a diluent.
- 15 23. A method of combating mycoses and bacterial infection in non-human animals which comprises administering to the animals an active compound according to any one of claims 1 to 10 and 17 either alone or in admixture with a diluent or in the form of a medicament according to claim 21 or 22.
- 20 24. A method according to claim 23 in which the active compound is administered in an amount of 8 to 500 mg per kg of body weight per day.
- 20 25. A method according to claim 23 or claim 24 in which the active compound is administered orally or locally.
- 25 26. A compound according to claim 1 as described in Example 36.
- 25 27. A composition, medicament or method according to any one of claims 18 to 25 wherein the said active ingredient, compound or active compound is the compound described in Example 36.

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