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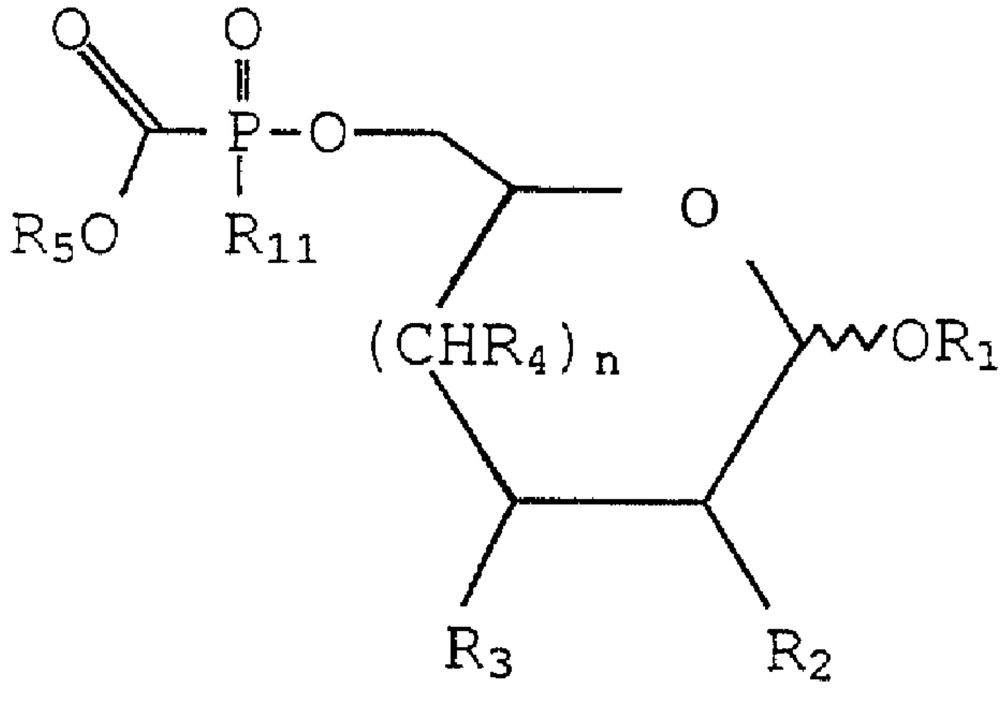
(54) Titre : UTILISATION DE DERIVES DE PHOSPHONOFORMATE POUR TRAITER DES INFECTIONS
(54) Title: USE OF PHOSPHONOFORMIC ACID DERIVATIVES FOR TREATING INFECTIONS



(I)

(57) Abrégé/Abstract:
The invention relates to the use of a compound of formula (I) for the prophylaxis and therapy of infectious processes in humans and animals, which processes are induced by bacteria, fungi or parasites. The inventive compound is also used as fungicidal, bactericidal or herbicidal agent in plants.

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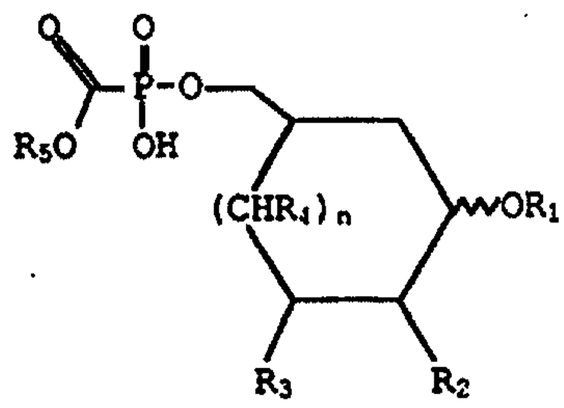
(54) Title: USE OF PHOSPHONOFORMIC ACID DERIVATIVES FOR TREATING INFECTIONS

(54) Bezeichnung: VERWENDUNG VON PHOSPHONOAMEISENSÄUREDERIVATEN ZUR BEHANDLUNG VON INFEKTIONEN



(I)

(57) Abstract

The invention relates to the use of a compound of formula (I) for the prophylaxis and therapy of infectious processes in humans and animals, which processes are induced by bacteria, fungi or parasites. The inventive compound is also used as fungicidal, bactericidal or herbicidal agent in plants.

(57) Zusammenfassung

Verwendung einer Verbindung der Formel (I), zur prophylaktischen und therapeutischen Behandlung von infektiösen Prozessen bei Mensch und Tier, die durch Bakterien, Pilze oder Parasiten hervorgerufen werden und als Fungizid, Bakterizid oder Herbizid bei Pflanzen.

Hassan Jomaa, Gießen

15747

Use of phosphonoformic acid derivatives for the treatment of infections

This invention relates to the use of phosphonoformic acid derivatives for the therapeutic and prophylactic treatment of infections in humans and animals caused by bacteria, fungi and parasites, and to the use thereof as a fungicide, bactericide and herbicide in plants. According to the invention, the phosphonoformic acid derivatives comprise the physiologically compatible salts, esters and amides.

Phosphonoformic acid derivatives are already known for their antiviral properties. Pharmaceutical preparations for treating viral infections have already been described in US patents 4 215 113, 4 665 062 and 4 771 041.

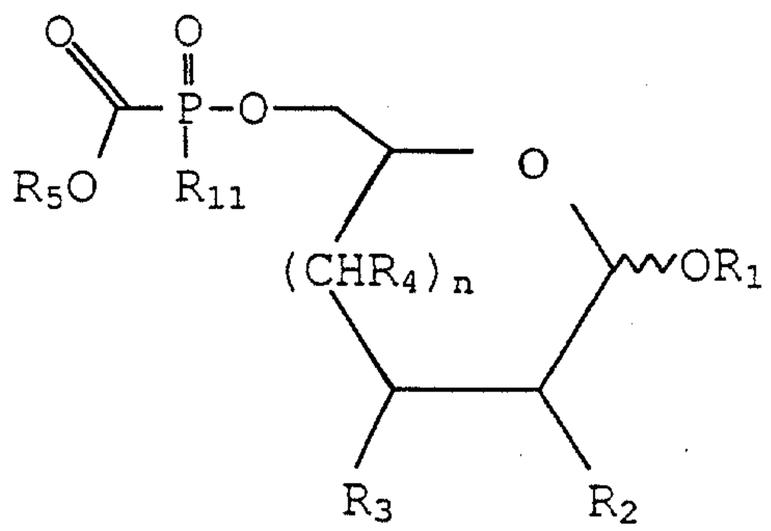
In particular, the antiviral action of phosphonoformic acid derivatives and the production thereof have already been described in WO 98/16537.

In order to widen the range of options for treating humans and animals and for protecting plants, there is an urgent requirement to provide agents which are not only highly active but, unlike other pharmaceutical preparations or phytosanitary agents, also exhibit reduced side-effects or reduced environmental impact and thus constitute a reduced risk to human health.

The object of the present invention is accordingly to provide a substance which is universally usable in infections by bacteria, fungi and parasites in humans and animals and as a fungicide, bactericide and herbicide in plants and which meets the above-stated requirements.

This object is utterly surprisingly achieved by the group of substances defined in claim 1. This group of substances exhibits both an antiinfective action against bacteria, fungi and uni- and multicellular parasites and a fungicidal, bactericidal and herbicidal action in plants.

The organophosphorus compounds used according to the invention are of the general formula (I):



(I)

in which the zigzag line represents a bond which has either α- or β-configuration,

n is 0 or 1,

in which R_{11} is selected from the group which consists of C_{1-26} alkyl residues, C_{2-26} alkenyl residues with 1 to 6 double bonds, C_{2-26} alkynyl residues with 1 to 6 triple bonds, C_{1-26} acyl residues, Ar-C_{0-26}-alkyl residues, C_{3-8}-cycloalkyl-C_{0-26}-alkyl residues, C_{3-8}-heterocycloalkyl-C_{0-26}-alkyl residues with one or two nitrogen, oxygen or sulfur atoms, halogen and OX_{11}, wherein all the above-stated residues may be substituted with C_{1-9} alkyl, C_{1-9} alkoxy, hydroxy, amino, halogen or oxo groups,
wherein X_{11} is selected from the group which consists of hydrogen, C_{1-26} alkyl residues, C_{2-26} alkenyl residues with 1 to 6 double bonds, C_{2-26} alkynyl residues with 1 to 6 triple bonds, Ar-C_{0-26}-alkyl residues, C_{3-8} cycloalkyl residues, C_{1-26} acyl residues, C_{3-8}-heterocycloalkyl-C_{0-26}-alkyl residues with one or two nitrogen, oxygen or sulfur atoms, C_{1-26} silyl residues, wherein all the above-stated residues may be substituted with C_{1-9} alkyl, C_{1-9} alkoxy, hydroxy, amino, halogen or oxo groups and consists of a cation of an organic and inorganic base, in particular a metal of main groups I, II or III of the periodic system, ammonium, substituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,

in which R_1 is selected from the group which consists of C_{1-24} alkyl residues, C_{2-24} alkenyl residues with 1 to 6 double bonds, C_{2-24} alkynyl residues with 1 to 6 triple bonds, C_{3-8} cycloalkyl residues, C_{3-8}-cycloalkyl-C_{1-24}-alkyl residues and C_{1-12}-alkoxy-C_{1-12}-alkyl residues, wherein all the residues may be branched or unbranched and may optionally be substituted with C_{1-9} alkyl, C_{1-9} alkoxy, hydroxy, amino, halogen or oxo groups,

in which R_2, R_3 and R_4 are each independently selected from the group which consists of hydrogen, halogen, amino, acetylamino, azido and XR_6 groups, wherein X is O or S and R_6 is selected from the group which consists of a hydrogen residue, branched or unbranched C_{1-4} alkyl residues and C_{2-4} alkenyl residues, wherein both the C_{1-4} alkyl residues and the C_{2-4}

alkenyl residues may optionally be substituted with hydrogen, amino, halogen or oxo groups, or

R_2, R_3 and R_4 together with the particular geminal hydrogen group denote an oxo group,

R_5 is selected from the group which consists of hydrogen, C_{1-24} alkyl residues, C_{3-8} cycloalkyl groups, Ar-(C_{0-24}-alkyl) residues, C_{3-8}-heterocycloalkyl-C_{0-24}-alkyl residues with one or two nitrogen, oxygen or sulfur atoms, halogen, wherein all the residues may be branched or unbranched and may optionally be substituted with hydroxy, amino, halogen, oxo groups, C_{1-4} alkyl groups, C_{1-4} alkoxy groups, formyl, acetyl, propionyl, butyryl groups and C_{2-5} alkoxycarbonyl groups or may contain 1-6 double or triple bonds, wherein, if R_5 is an Ar-(C_{1-24}-alkyl) group, two adjacent alkyl residues or alkoxy residues may also form a 5-6-membered cyclic ring, or

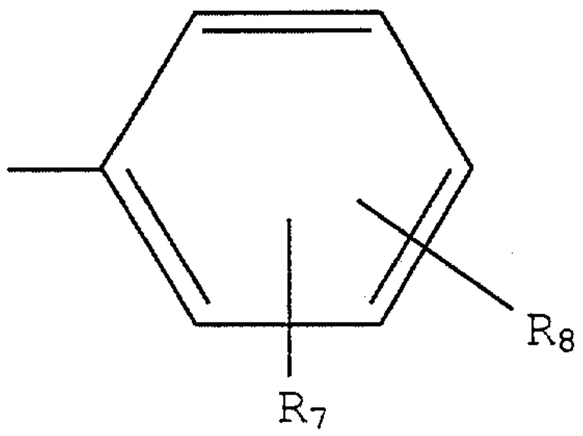
R_5 is selected from the group which consists of $R_9COOCHR_{10}$ and $R_9OCOOCHR_{10}$, wherein R_9 is selected from the group which consists of C_{1-6} alkyl residues, C_{2-6} alkenyl residues, C_{2-6} alkynyl residues, C_{3-8} cycloalkyl residues, C_{3-8}-cycloalkyl-C_{1-6}-alkyl residues and C_{1-6}-alkoxy-C_{1-6}-alkyl residues, wherein all the residues may be branched or unbranched and may optionally be substituted with hydroxy, amino, halogen or oxo groups, and

R_{10} is a branched or unbranched C_{1-4} alkyl residue,

and wherein the configurations of the substituents R_2, R_3, R_4 and $R_5OOCPO(OH)OCH_2$ in I are independently from among D-gluco, L-gluco, D-galacto, L-galacto, D-manno, L-manno, D-talo, L-talo, D-allo, L-allo, D-altro, L-altro, D-gulo, L-gulo, D-ido or L-ido, if n is 1, or the configurations of the substituents R_2, R_3 and $R_5OOCPO(OH)OCH_2$ in I are independently from among D-ribo, L-ribo, D-arabino, L-arabino, D-xylo, L-xylo, D-lyxo or L-lyxo, if n is 0.

The glycosidic bond in the compounds according to the invention is preferably in α.

configuration.It is furthermore preferred that R_5 is a phenyl residue of the formula II or III,



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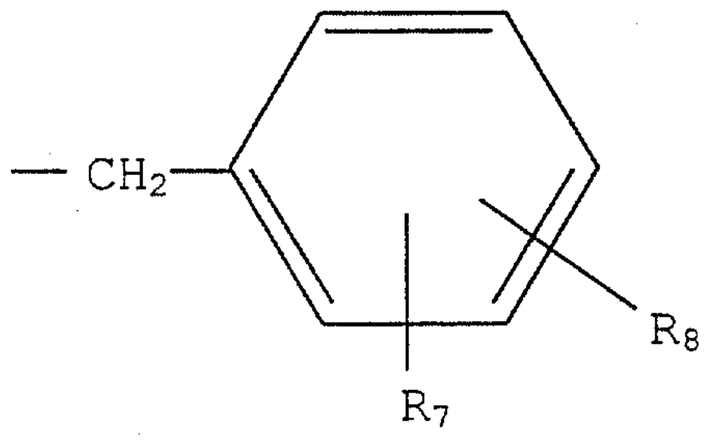


(III)

wherein R_7 and R_8 are identical or different and are attached to the phenyl ring at any two positions and are each independently selected from the group which consists of hydrogen, halogen, C_{1-4} alkyl residues, C_{1-4} alkoxy residues, formyl, acetyl, propionyl, butyryl residues, formyloxy, acetyloxy, propionyloxy, butyryloxy residues, C_{2-5} alkoxycarbonyl residues, all of which may be branched or unbranched, or
R_7 and R_8 together form an unbranched saturated alkylene chain with 3 to 4 carbon atoms, which is attached to adjacent positions, for example the 2,3 positions or 3,4 positions of the phenyl ring or
R_7 and R_8 together form a methylenedioxy residue, a 1,1-ethylidenedioxy residue, 1,1-ethenylenedioxy residue, a 1,1-ethylenedioxy residue or a 1,2-ethylenedioxy residue, which are attached to the 2,3 or 3,4 positions of the phenyl ring.

Preferred compounds of the formula I are moreover those in which R_1 is selected from the group which consists of C_{9-24} alkyl residues, C_{9-24} alkenyl residues with 1 to 6 double bonds, C_{9-24} alkynyl residues with 1 to 6 triple bonds, C_{3-8}-cycloalkyl-C_{6-24}-alkyl residues and C_{1-2}-alkoxy-C_{8-12}-alkyl residues, each of which may optionally be branched or unbranched and may be substituted with hydrogen, amino, halogen or oxo residues.

In particular, it is preferred to use those compounds in which R_1 is selected from the group which consists of an *n*-tetradecyl residue, *n*-octadecyl residue, a *trans*-9-octadecen-1-yl residue and a *cis*-9-octadecen-1-yl residue. R_2, R_3, R_4 are preferably each a hydroxy group. R_5 is preferably a hydrogen. Moreover, n is preferably 1 and the configuration of the substituents R_2, R_3, R_4 and $R_5OOCPO(OH)OCH_2$ is D-gluco.

R_{11} preferably denotes OX_{11} where X_{11} = hydrogen.
Suitable examples of acyl groups are stated below.
Aliphatic acyl groups are defined as acyl residues originating from an aliphatic acid and include the following:
alkanoyl (for example formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl etc.); alkenoyl (for example acryloyl, methacryloyl, crotonoyl etc.); alkylthioalkanoyl (for example methylthioacetyl, ethylthioacetyl etc.); alkanesulfonyl (for

example mesyl, ethanesulfonyl, propanesulfonyl etc.); alkoxycarbonyl (for example methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl etc.); alkylcarbamoyl (for example methylcarbamoyl etc.); (N-alkyl)thiocarbamoyl (for example (N-methyl)thiocarbamoyl etc.); alkylcarbamimidoyl (for example methylcarbamimidoyl etc.); oxalo; alkoxalyl (for example methoxalyl, ethoxalyl, propoxalyl etc.).

In the above examples of aliphatic acyl groups, the aliphatic hydrocarbon moiety, in particular the alkyl group or alkane residue, may optionally have one or more suitable substituents, such as amino, halogen (for example fluorine, chlorine, bromine etc.), hydroxy, hydroxyimino, carboxy, alkoxy (for example methoxy, ethoxy, propoxy etc.), alkoxycarbonyl, acylamino (for example benzyloxycarbonylamino etc.), acyloxy (for example acetoxy, benzoyloxy etc.) and the like; preferred aliphatic acyl residues with such substituents which may be mentioned are, for example, alkanoyls substituted with amino, carboxy, amino and carboxy, halogen, acylamino or the like.

Aromatic acyl residues are defined as those acyl residues which originate from an acid with a substituted or unsubstituted aryl group, wherein the aryl group may comprise phenyl, toluyl, xylyl, naphthyl and the like; suitable examples are stated below:
aroyl (for example benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl etc.); aralkanoyl (for example phenylacetyl etc.); aralkenoyl (for example cinnamoyl etc.); aryloxyalkanoyl (for example phenoxyacetyl etc.);
arylthioalkanoyl (for example phenylthioacetyl etc.); arylaminoalkanoyl (for example N-phenylglycyl etc.); arenesulfonyl (for example benzenesulfonyl, tosyl or toluenesulfonyl, naphthalenesulfonyl etc.); aryloxycarbonyl (for example phenoxycarbonyl, naphthyloxycarbonyl etc.); aralkoxycarbonyl (for example benzyloxycarbonyl etc.); arylcarbamoyl (for example phenylcarbamoyl, naphthylcarbamoyl etc.); arylglyoxyloyl (for example phenylglyoxyloyl etc.).

In the above-stated Examples of aromatic acyl residues, the aromatic hydrocarbon moiety (in particular the aryl residue) and/or the aliphatic hydrocarbon moiety (in particular the alkane residue) may optionally have one or more suitable substituents, such as those which have already been stated as suitable substituents for the alkyl group or the alkane residue.
Examples of preferred aromatic acyl residues with specific substituents which may in particular be mentioned are aroyl substituted with halogen and hydroxy or with halogen and aralkanoyl substituted with hydroxy, hydroxyimino, dihaloalkanoyloxyimino, together with
arylthiocarbamoyl (for example phenylthiocarbamoyl etc.);
arylcarbamimidoyl (for example phenylcarbamimidoyl etc.).

A heterocyclic acyl residue is taken to mean an acyl residue which originates from an acid with a heterocyclic group; such residues include:

heterocyclic carbonyl, in which the heterocyclic residue is an aromatic or aliphatic 5- to 6-membered heterocycle with at least one heteroatom from the group nitrogen, oxygen and sulfur (for example thiophenyl, furoyl, pyrrolecarbonyl, nicotinyl etc.);

heterocycle-alkanoyl, in which the heterocyclic residue is 5- to 6-membered and comprises at least one heteroatom from the group nitrogen, oxygen and sulfur (for example thiophenylacetyl, furylacetyl, imidazolylpropionyl, tetrazolylacetyl, 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetyl etc.) and the like.

In the above Examples of heterocyclic acyl residues, the heterocycle and/or the aliphatic hydrocarbon moiety may optionally comprise one or more suitable substituents, such as the same as were stated to be suitable for alkyl and alkane groups.

Aryl is an aromatic hydrocarbon residue, such as phenyl, naphthyl etc., which may optionally comprise one or more suitable substituents, such as alkyl, alkenyl, alkynyl, alkoxy (for example methoxy, ethoxy etc.), halogen (for example fluorine, chlorine, bromine etc.), nitro and the like.

"Aralkyl" includes mono-, di-, triphenylalkyls such as benzoyl, phenethyl, benzhydryl, trityl and the like, wherein the aromatic moiety may optionally comprise one or more suitable substituents, such as alkoxy (for example methoxy, ethoxy etc.), halogen (for example. fluorine, chlorine, bromine etc.), nitro and the like.

WO 98/16537 provides a comprehensive description of a production process for these compounds.

The organophosphorus compounds are in particular suitable for the therapeutic and prophylactic treatment of infections in humans and animals caused by bacteria, uni- and multicellular parasites and fungi.

The compounds are active against unicellular parasites (protozoa), in particular against the causative organisms of malaria and sleeping sickness and of Chagas' disease, toxoplasmosis, amoebic dysentery, leishmaniases, trichomoniasis, pneumocystosis, balantidiasis, cryptosporidiosis, sarcocytosis, acanthamoebosis, naeglerosis, coccidiosis, giardiasis and lambliasis.

They are accordingly in particular suitable for the prophylactic treatment of malaria and of sleeping sickness and of Chagas' disease, of toxoplasmosis, amoebic dysentery, leishmaniases, trichomoniasis, pneumocystosis, balantidiasis, cryptosporidiosis, sarcocytosis, acanthamoebosis, naeglerosis, coccidiosis, giardiasis and lambliasis.

The active substances according to the invention may in particular be used against the following bacteria:
bacteria of the family Propionibacteriaceae, in particular of the genus Propionibacterium, in particular the species Propionibacterium acnes, bacteria of the family Actinomycetaceae, in particular of the genus Actinomyces, bacteria of the genus Cornynebacterium, in particular the species Corynebacterium diphtheriae and Corynebacterium pseudotuberculosis, bacteria of the family Mycobacteriaceae, of the genus Mycobacterium, in particular the species Mycobacterium leprae, Mycobacterium tuberculosis, Mycobacterium bovis and Mycobacterium avium, bacteria of the family Chlamydiaceae, in particular the species Chlamydia trachomatis and Chlamydia psittaci, bacteria of the genus Listeria, in particular the species Listeria monocytogenes, bacteria of the species Erysipelthrix rhusiopathiae, bacteria of the genus Clostridium, bacteria of the genus Yersinia, the species Yersinia pestis, Yersinia pseudotuberculosis, Yersinia enterocolitica and Yersinia ruckeri, bacteria of the family Mycoplasmataceae, of the genera Mycoplasma and Ureaplasma, in particular the species Mycoplasma pneumoniae, bacteria of the genus Brucella, bacteria of the genus Bordetella, bacteria of the family Neisseriaceae, in particular of the genera Neisseria and Moraxella, in particular the species Neisseria meningitides, Neisseria gonorrhoeae and Moraxella bovis, bacteria of the family Vibrionaceae, in particular of the genera Vibrio, Aeromonas, Plesiomonas and Photobacterium, in particular the species Vibrio cholerae, Vibrio anguillarum and Aeromonas salmonicidas, bacteria of the genus Campylobacter, in particular the species Campylobacter jejuni, Campylobacter coli and Campylobacter fetus, bacteria of the genus Helicobacter, in particular the species Helicobacter pylori, bacteria of the families Spirochaetaceae and Leptospiraceae, in particular of the genera Treponema, Borrelia and Leptospira, in particular Borrelia burgdorferi, bacteria of the genus Actinobacillus, bacteria of the family Legionellaceae, of the genus Legionella, bacteria of the family Rickettsiaceae and family Bartonellaceae, bacteria of the genera Nocardia and Rhodococcus, bacteria of the genus Dermatophilus, bacteria of the family Pseudomonadaceae, in particular of the genera Pseudomonas and Xanthomonas, bacteria of the family Enterobacteriaceae, in particular of the genera Escherichia, Klebsiella, Proteus, Providencia, Salmonella, Serratia and Shigella, bacteria of the family Pasteurellaceae, in particular of the genus Haemophilus, bacteria of the family Micrococcaceae, in particular of the genera Micrococcus and Staphylococcus, bacteria of the family Streptococcaceae, in particular of the genera Streptococcus and Enterococcus and bacteria of the family Bacillaceae, in particular of the genera Bacillus and Clostridium.

Organophosphorus compounds and the derivatives thereof are consequently suitable for treating diphtheria, acne vulgaris, listerioses, swine erysipelas in animals, gas gangrene in humans and animals, malignant oedema in humans and animals, tuberculosis in humans and animals, leprosy and further mycobacterioses in humans and animals, paratuberculosis in animals, plague, mesenterial lymphadenitis and pseudotuberculosis in humans and animals, cholera, legionnaires' disease, borreliosis in humans and animals, leptospiroses in humans and animals, syphilis, Campylobacter enteritis infections in humans and animals, Moraxella keratoconjunctivitis and serositis in animals, brucellosis of animals and humans, anthrax in humans and animals, actinomycosis in humans and animals, streptotrichoses, psittacosis/ortnithosis in animals, Q fever, ehrlichiosis.

Use is furthermore effective in the eradication of Helicobacter in ulcers of the gastrointestinal tract.

Combinations with another antibiotic may also be used to treat the above-stated diseases. Isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, protionamide and dapsone are in particular suitable for combination preparations with other antiinfective agents for the treatment of tuberculosis.

The described compounds, i.e. the organophosphorus compounds of the formulae I and esters and amides and salts thereof exhibit strong cytotoxic activity against uni- and multicellular parasites, in particular against the causative organisms of malaria and sleeping sickness. The compounds used according to the invention are accordingly usable for the treatment of infective diseases which are caused in humans and animals by bacteria, parasites and fungi. The compounds are also suitable for the prevention of diseases which are caused by bacteria, parasites and fungi.

The organophosphorus compounds used according to the invention, which generally include for this purpose pharmaceutically acceptable salts, amides, esters, a salt of such an ester or also compounds which, on administration, provide the compounds used according to the invention as metabolites or breakdown products (also known as "prodrugs"), may be formulated for administration in any suitable manner analogous to known agents having an antiinfective action (mixed with a non-toxic, pharmaceutically acceptable excipient).

Pharmaceutically acceptable salts of the compounds include salts which the compounds of the formula I used according to the invention form in their protonated form as an ammonium salt of inorganic or organic acids, such as hydrochloric acid, sulfuric acid, citric acid, maleic acid, fumaric acid, tartaric acid, p-toluenesulfonic acid.

Salts are also particularly pharmaceutically suitable, such as sodium salt, potassium salt, calcium salt, ammonium salt, ethanolamine salt, triethylamine salt, dicyclohexylamine salt and salts of an amino acid, such as arginine salt, aspartic acid salt, glutamic acid salt.

The activity of the substances is determined using a test system. This system is based upon in vitro measurement of the inhibition of growth of bacteria, parasites, fungi or plants. Test methods known to the person skilled in the art are in part used for this purpose.

For example, antimalarial activity is determined by measuring the inhibition of the growth of malaria parasites in blood cultures.

Antibacterial activity is determined on the basis of measuring the inhibition of bacterial growth on nutrient media and in liquid cultures.

Fungicidal activity is determined on the basis of inhibition of fungal growth on nutrient media and in liquid cultures.

Some of the microorganisms which are to be investigated may only be investigated in animal models. In this case, the appropriate models will be used.

Substances which exhibit activity in in vitro measurement systems are then further investigated in in vivo models.
Antiparasitic, fungicidal or antibacterial activity is further evaluated in the appropriate animal models.

Screening for herbicidal activity is determined by means of algal systems and measurement of isoprene emissions from plants under standard conditions.

The pharmaceutically active agents may be prepared in dosage units in the form of pharmaceutical preparations. This means that the preparation is in the form of individual components, for example tablets, coated tablets, capsules, pills, suppositories and ampoules, the active substance content of which corresponds to a fraction or multiple of an individual dose. The dosage units may contain, for example 1, 2, 3 or 4 individual doses or 1/2, 1/3 or 1/4 of an individual dose. An individual dose preferably contains the quantity of active substance which is administered at one time and usually corresponds to a whole, half, third or quarter of a daily dose.

Non-toxic, inert, pharmaceutically suitable excipients should be taken to mean solid, semi-solid or liquid diluents, fillers and formulation auxiliaries of all kinds.

Preferred pharmaceutical preparations which may be mentioned are tablets, coated tablets, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays. Tablets, coated tablets, capsules, pills and granules may contains the active substances together with conventional excipients, such as (a) fillers and extenders, for example starches, lactose, cane sugar, glucose, mannitol and silica, (b) binders, for example carboxymethylcellulose, alginates, gelatine, polyvinylpyrrolidone, (c) humectants, for example glycerol, (d) suspending agents, for example agar-agar, calcium carbonate and sodium carbonate, (e) dissolution retardants, for example paraffin and (f) resorption accelerators, for example quaternary ammonium compounds, (g) wetting agents, for example cetyl alcohol, glycerol monostearate, (h) adsorbents, for example kaolin and bentonite and (i) lubricants, for example talcum, calcium and magnesium stearate and solid polyethylene glycols or mixtures of the substances stated in (a) to (i).

The tablets, coated tablets, capsules, pills and granules may be provided with conventional coatings and shells optionally containing opacifying agents and may also be composed such that they release the active substances only with a delay or preferably in a particular part of the intestinal tract, wherein polymeric substances and waxes may, for example, be used as the matrices.

The active substance or substances, optionally together with one or more of the above-stated excipients, may also be present in microencapsulated form.

In addition to the active substance or substances, suppositories may contain conventional water-soluble or water-insoluble excipients, for example polyethylene glycols, fats, for example cocoa butter and higher esters (for example C14 alcohol with C16 fatty acid) or mixtures of these substances.

In addition to the active substance or substances, ointments, pastes, creams and gels may contain conventional excipients, for example animal and vegetable fats, waxes, paraffins, starch, gum tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silica, talcum and zinc oxide or mixtures of these substances.

In addition to the active substance or substances, powders and sprays may contain conventional excipients, for example lactose, talcum, silica, aluminium hydroxide, calcium silicate and polyamide powder or mixtures of these substances. Sprays may additionally contain conventional propellants, for example chlorofluorocarbons.

In addition to the active substance or substances, solutions and emulsions may contain conventional excipients, such as solvents, solubilising agents and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular cottonseed oil, peanut oil, corn oil, olive oil, castor oil and sesame oil, glycerol, glycerol formal, tetrahydrofurfuryl alcohol, polyethylene glycols and sorbitan fatty acid esters or mixtures of these substances.

For parenteral administration, the solutions and emulsions may also be present in sterile, isotonic form.

In addition to the active substance or substances, suspensions may contain conventional excipients, such as liquid diluents, for example water, ethyl alcohol, propylene glycol, suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and gum tragacanth or mixtures of these substances.

The stated formulations may also contain colorants, preservatives and odour- or flavour-enhanced additives, for example peppermint oil and eucalyptus oil, and sweeteners, for example saccharin.

The active substances of the formula I should preferably be present in the pharmaceutical preparations listed above in a concentration of approx. 0.1 to 99.5 wt.%, preferably from approx. 0.5 to 95 wt.%, of the complete mixture.

Apart from the compounds of the formula I, the pharmaceutical preparations may also contain further pharmaceutical active substances.

The compounds may be used together with hitherto described substances having antibacterial, antimycotic and antiparasitic properties. Such substances in particular include compounds which have already been used in therapeutic applications or are still used. Substances which are suitable for this purpose are in particular those listed in the Red List or in Simon/Stille, Antibiokia-Therapie in Klinik und Praxis, 9th edition, 1998, Schatauer Verlag, or on the Internet at http://www.customs.treas.gov/imp-exp/rulings/harmoniz/hrm129.html. The derivatives may in particular be present with penicillins, benzylpenicillin (penicillin G), phenoxypenicillins, isoxazolylpenicillins, aminopenicillins, ampicillin, amoxicillin, bacampicillin, carboxypenicillin, ticarcillin, temocillin, acylaminopenicillins, azlocillin, mezlocillin, piperacillin, apalcillin, mecillinam, cephalosporins, cefazolin group, cefuroxime group, cefoxitin group, cefoxitin, cefotetan, cefmetazole, latamoxef, flomoxef, cefotaxime

group, cefozidime, ceftazidime group, ceftazidime, cefpirome, cefepime, conventional cephalosporins, cefsulodin, cefoperazone, oral cephalosporins of the cephalexin group, loracarbef, cefprozil, new broad-spectrum oral cephalosporins, cefixime, cefpodoxime-proxetil, cefuroxime-axetil, cefetamet, cefotiam-hexetil, cefdinir, ceftibuten, other ß-lactam antibiotics, carbapenem, imipenem/cilastatin, meropenem, biapenem, aztreonam, ß-lactamase inhibitors, clavulanic acid/amoxicillin, clavulanic acid/ticarcillin, sulbactam/ampicillin, tazobactam/piperacillin, tetracyclines, oxytetracycline, rolitetracycline, doxycycline, minocycline, chloramphenicol, aminoglycosides, gentamicin, tobramycin, netilmicin, amikacin, spectinomycin, macrolides, erythromycin, clarithromycin, roxithromycin, azithromycin, dirithromycin, spiramycin, josamycin, lincosamides, clindamycin, fusidic acid, glycopeptide antibiotics, vancomycin, teicoplanin, pristinamycin derivatives, fosfomycin, antimicrobial folic acid antagonists, sulfonamides, co-trimoxazole, trimethoprim, other diaminopyrimidine-sulfonamide combinations, nitrofurans, nitrofurantoin, nitrofurazone, gyrase inhibitors (quinolones), norfloxacin, ciprofloxacin, ofloxacin, sparfloxacin, enoxacin, fleroxacin, pefloxacin, lomefloxacin, Bay Y3118, nitroimidazoles, antimycobacterial agents, isoniazid, rifampicin, rifabutin, ethambutol, pyrazinamide, streptomycin, capreomycin, prothionamide, terizidone, dapsone, clofazimine, topical antibiotics, bacitracin, tyrothricin, polymyxins, neomycin, kanamycin, paromomycin, mupirocin, antiviral agents, acyclovir, ganciclovir, azidothymidine, didanosine, zalcitabine, thiacytidine, stavudine, ribavirin, idoxuridine, trifluridine, foscarnet, amantadine, interferons, tibol derivatives, proteinase inhibitors, antimycotics, polyenes, amphotericin B, nystatin, natamycin, azoles, azoles for septic therapy, miconazole, ketoconazole, itraconazole, fluconazole, UK-109,496, azoles for topical use, clotrimazole, econazole, isoconazole, oxiconazole, bifonazole, flucytosine, griseofulvin, ciclopirox olamine, tolnafnate, naftifine, terbinafine, amorolfine, anthraquinones, betulinic acid, semianthraquinones, xanthones, naphthoquinones, arylamino alcohols, quinine, quinidines, mefloquine, halofantrine, chloroquine, amodiaquine, acridine, benzonaphthyridine, mepacrine, pyronaridine, dapsone, sulfonamides, sulfadoxine, sulfalenes, trimethoprim, proguanil, chlorproguanil, diaminopyrimidines, pyrimethamine, primaquine, aminoquinolines, WR 238,605, tetracycline, doxycycline, clindamycin, norfloxacin, ciprofloxacin, ofloxacin, artemisinin, dihydroartemisinin, 10b artemether, arteether, atresunate, atovaquone, suramin, melarsoprol, nifurtimox, stibogluconate sodium, pentamidine, amphotericin B, metronidazole, clioquinol, mebendazole, niclosamide, praziquantel, pyrantel, tiabendazole, diethylcarbamazine, ivermectin, bithionol, oxamniquine, metrifonate, piperazine, embonate.

The organophosphorus compounds may furthermore be present in the pharmaceutical preparations in combination with sulfonamide, sulfadoxine, artemisinin, atovaquone, quinine, chloroquine, hydroxychloroquine, mefloquine, halofantrine, pyrimethamine, armesin, tetracyclines, doxycycline, proguanil, metronidazole, praziquantel, niclosamide, mebendazole,

pyrantel, tiabendazole, diethylcarbazine, piperazine, pyrivinium, metrifonate, oxamniquine, bithionol or suramin or two or more of these substances.

The above-stated pharmaceutical preparations are produced in the conventional manner using known methods, for example by mixing the active substance or substances with the excipient or excipients.

The stated preparations may be administered to humans and animals orally, rectally, parenterally (intravenously, intramuscularly, subcutaneously), intracisternally, intravaginally, intraperitoneally, topically (powders, ointments, drops) and for the treatment of infections in cavities, body cavities. Suitable preparations which may be considered are solutions for injections, solutions and suspensions for oral therapy, gels, infusion formulations, emulsions, ointments or drops. Topical treatment may be performed using ophthalmological and dermatological formulations, silver and other salts, ear drops, eye ointments, powders or solutions. Administration to animals may also be achieved via the feed or drinking water in suitable formulations. Gels, pulverulent formulations, powders, tablets, controlled-release tablets, premixes, concentrates, granules, pellets, tablets, boli, capsules, aerosols, sprays, inhalation formulations may also be used in humans and animals. The compounds used according to the invention may also be incorporated into other supports, such as for example plastics (plastic chains for topical treatment), collagen or bone cement.

It has in general proved advantageous in both human and veterinary medicine to administer the active substances of the formula I in total quantities of approx. 0.05 to approx. 2000, preferably of 5 to 1000 mg/kg body weight per 24 hours, optionally in the form of two or more individual doses in order to achieve the desired results. An individual dose preferably contains the active substance or substances in quantities of approx. 0.25 to approx. 2000 mg, which are administered, for example, 1 to 4 times daily. It may, however, be necessary to deviate from the stated dosages, in particular as a function of the nature and body weight of the patient to be treated, the nature and severity of the disease, the nature of the preparations and the route of administration of the pharmaceutical preparation and the period of time over which administration is performed.

Liquid preparations may be administered in the form of solutions, syrups, emulsions or suspensions, which, for oral administration, contain for example 0.1 to 50 wt.% of active substance. In the case of topical administration in the form of solutions, gels, suspension or the like, the active substance preferably amounts to between =0.05 and 20 wt.% of the preparation.

In some cases, it may accordingly be sufficient to use less than the above-stated quantity of active substance, while in other cases more than the above-stated quantity of active substance must be used. The person skilled in the art will use his/her skill to determine the optimum dosage and route of administration required in each particular case.

The compounds used according to the invention may be given to animals in conventional concentrations and preparations together with feed or feed preparations or with drinking water.

The compounds used according to the invention are furthermore ideally usable as bactericides, fungicides and herbicides in plants.

Example

The following substances are tested for antimalarial activity:

Disodium *n*-octadecyl-α-D-glycopyranosid-6-yl carboxyphosphonate	Substance 1
Disodium *cis*-9-octadecen-1-yl-α-D-glycopyranosid-6-yl carboxyphosphonate	Substance 2
Disodium *trans*-9-octadecen-1-yl-α-D-glycopyranosid-6-yl carboxyphosphonate	Substance 3
Disodium *n*-tetradecyl-α-D-glycopyranosid-6-yl carboxyphosphonate	Substance 4
Disodium *n*-tetradecyl-β-D-glycopyranosid-6-yl carboxyphosphonate	Substance 5
Disodium *n*-dodecyl-α-D-glycopyranosid-6-yl carboxyphosphonate	Substance 6
Disodium *n*-eicosyl-β-D-galactopyranosid-6-yl carboxyphosphonate	Substance 7

The antimalarial activity of substances 1 to 7 was tested on mice which had been infected with the murine malaria pathogen Plasmodium vinckei. The test was performed in accordance with a modified Peters protocol [W. Peters, Malaria, J.P. Kreier, Ed., Academic Press, New York 1980, Vol. 1, pages 160-161]. To this end, mice were each infected on day 0 with 10^7 infected erythrocytes by intraperitoneal (i.p.) injection. Successful infection was confirmed on day 1 by Giemsa-stained blood smears. Treatment was performed on days 1 to 4 by twice daily i.p. injections of various doses of the substances. Three to four mice were treated at each dose. On day 5, the blood parasite contents of the treated mice and untreated controls were determined by blood smears. The percentage decrease in blood parasite contents of the treated animals relative to the controls was calculated. These data were used to extrapolate to the concentration of the drug at which the blood parasite content falls to 50% (ED50).

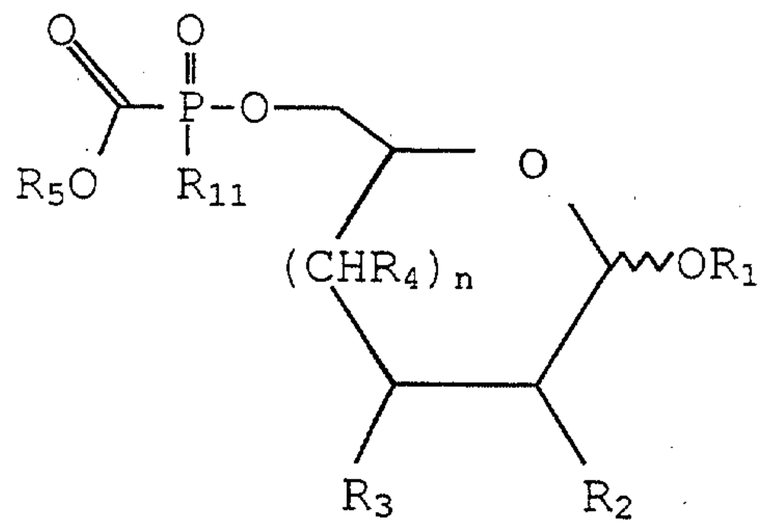
The results, i.e. ED50 values, are listed in the following table:

Table

Substance no.	ED50/(mg/kg)
1	240
2	320
3	570
4	180
5	280
6	370
7	420

Patent Claims

1. Use of a compound of the formula I



(I)

in which the zigzag line represents a bond which has either α- or β-configuration,

in which n is 0 or 1,

in which R_{11} is selected from the group which consists of C_{1-26} alkyl residues, C_{2-26} alkenyl residues with 1 to 6 double bonds, C_{2-26} alkynyl residues with 1 to 6 triple bonds, C_{1-26} acyl residues, Ar-C_{0-26}-alkyl residues, C_{3-8}-cycloalkyl-C_{0-26}-alkyl residues, C_{3-8}-heterocycloalkyl-C_{0-26}-alkyl residues with one or two nitrogen, oxygen or sulfur atoms, halogen and OX_{11}, wherein all the above-stated residues may be substituted with C_{1-9} alkyl, C_{1-9} alkoxy, hydroxy, amino, halogen or oxo groups,
wherein X_{11} is selected from the group which consists of hydrogen, C_{1-26} alkyl residues, C_{2-26} alkenyl residues with 1 to 6 double bonds, C_{2-26} alkynyl residues with 1 to 6 triple bonds, Ar-C_{0-26}-alkyl residues, C_{3-8} cycloalkyl residues, C_{1-26} acyl residues, C_{3-8}-heterocycloalkyl-C_{0-26}-alkyl residues with one or two nitrogen, oxygen or sulfur atoms, C_{1-26} silyl residues, wherein all the above-stated residues may be substituted with C_{1-9} alkyl, C_{1-9} alkoxy, hydroxy, amino, halogen or oxo groups and consists of a cation of an organic and inorganic base, in particular a metal of main groups I, II or III of the periodic system, ammonium, substituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,

in which R_1 is selected from the group which consists of C_{1-24} alkyl residues, C_{2-24} alkenyl residues with 1 to 6 double bonds, C_{2-24} alkynyl residues with 1 to 6 triple bonds, C_{3-8} cycloalkyl residues, C_{3-8}-cycloalkyl-C_{1-24}-alkyl residues and C_{1-12}-alkoxy-C_{1-12}-alkyl residues, wherein all the residues may be branched or unbranched and may optionally be substituted with C_1

$_{-9}$ alkyl, C_{1-9} alkoxy, hydroxy, amino, halogen or oxy groups,

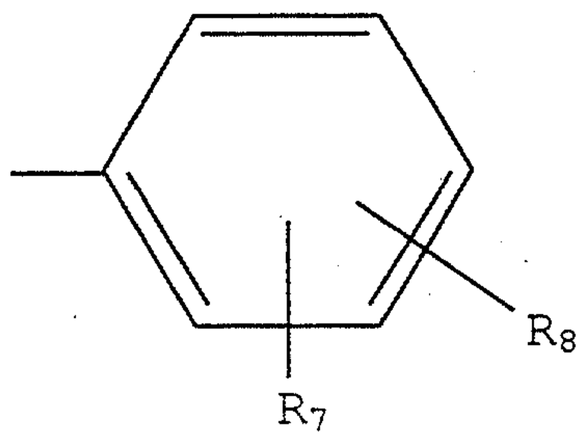
in which R_2, R_3 and R_4 are each independently selected from the group which consists of hydrogen, halogen, amino, acetylamino, azido and XR_6 groups, wherein X is O or S and R_6 is selected from the group which consists of a hydrogen residue, branched or unbranched C_{1-4} alkyl residues and C_{2-4} alkenyl residues, wherein both the C_{1-4} alkyl residues and the C_{2-4} alkenyl residues may optionally be substituted with hydrogen, amino, halogen or oxo groups, or
R_2, R_3 and R_4 together with the particular geminal hydrogen group denote an oxo group,

R_5 is selected from the group which consists of hydrogen, C_{1-24} alkyl residues, C_{3-8} cycloalkyl residues, Ar-(C_{0-24}-alkyl) residues, C_{3-8}-heterocycloalkyl-C_{0-24}-alkyl residues with one or two nitrogen, oxygen or sulfur atoms, halogen, wherein all the residues may be branched or unbranched and may optionally be substituted with hydroxy, amino, halogen, oxo groups, C_{1-4} alkyl groups, C_{1-4} alkoxy groups, formyl, acetyl, propionyl, butyryl groups and C_{2-5} alkoxycarbonyl groups or may contain 1-6 double or triple bonds, wherein, if R_5 is an Ar-(C_{1-24}-alkyl) group, two adjacent alkyl residues or alkoxy residues may also form a 5-6-membered cyclic ring, or
R_5 is selected from the group which consists of $R_9COOCHR_{10}$ and $R_9OCOOCHR_{10}$, wherein R_9 is selected from the group which consists of C_{1-6} alkyl residues, C_{2-6} alkenyl residues, C_{2-6} alkynyl residues, C_{3-8} cycloalkyl residues, C_{3-8}-cycloalkyl-C_{1-6}-alkyl residues and C_{1-6}-alkoxy-C_{1-6}-alkyl residues, wherein all the residues may be branched or unbranched and may optionally be substituted with hydroxy, amino, halogen or oxo groups, and
R_{10} is a branched or unbranched C_{1-4} alkyl residue,

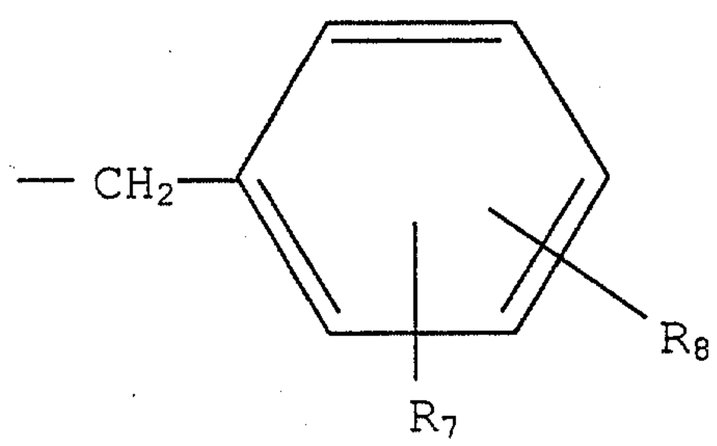
and in which the configurations of the substituents R_2, R_3, R_4 and $R_5OOCPO(OH)OCH_2$ in I are independently from among D-gluco, L-gluco, D-galacto, L-galacto, D-manno, L-manno, D-talo, L-talo, D-allo, L-allo, D-altro, L-altro, D-gulo, L-gulo, D-ido or L-ido, if n is 1, or
the configurations of the substituents R_2, R_3 and $R_5OOCPO(OH)OCH_2$ in I are independently from among D-ribo, L-ribo, D-arabino, L-arabino, D-xylo, L-xylo, D-lyxo or L-lyxo, if n is 0.
and the pharmaceutically acceptable salts, esters and amides thereof and salts of the esters and the optical isomers thereof

for the production of a pharmaceutical preparation for the prophylactic and therapeutic treatment of infectious processes in humans and animals which are caused by bacteria, fungi or parasites and as a fungicide, bactericide or herbicide in plants.

2. Use according to claim 1, characterised in that R_5 is a phenyl residue of the formula II or III,



(II)



(III)

wherein R_7 and R_8 are identical or different and are attached to the phenyl ring at any two positions and are each independently selected from the group which consists of hydrogen, halogen, C_{1-4} alkyl residues, C_{1-4} alkoxy residues, formyl, acetyl, propionyl, butyryl residues, formyloxy, acetyloxy, propionyloxy, butyryloxy residues, C_{2-5} alkoxycarbonyl residues, all of which may be branched or unbranched, or
R_7 and R_8 together form an unbranched saturated alkylene chain with 3 to 4 carbon atoms, which is attached to adjacent positions, for example the 2,3 positions or 3,4 positions of the phenyl ring or
R_7 and R_8 together form a methylenedioxy residue, a 1,1-ethenylenedioxy residue, a 1,1-ethylidenedioxy residue, a 1,1-ethylenedioxy residue or a 1,2-ethylenedioxy residue, which are attached to the 2,3 or 3,4 positions of the phenyl ring.

3. Use according to claim 1, characterised in that R_5 is a hydrogen.

4. Use according to one of claims 1 to 3, wherein R_1 is selected from the group which consists of C_{9-24} alkyl residues, C_{9-24} alkenyl residues with 1 to 6 double bonds, C_{9-24} alkynyl residues, C_{3-8}-cycloalkyl$_{6-24}$-alkyl residues and C_{1-12}-alkoxy$_{8-12}$-alkyl residues.

5. Use according to claim 4, wherein R_1 is selected from the group which consists of an *n*-tetradecyl residue, *n*-octadecyl residue, a *trans*-9-octadecen-1-yl residue and a *cis*-9-octadecen-1-yl residue.

6. Use according to one of the preceding claims, wherein R_2, R_3, R_4 are each a hydroxy group.

7. Use according to one of the preceding claims, wherein the glycosidic bond is in α configuration.

8. Use according to one of claims 1 to 6, wherein the glycosidic bond is in β configuration.

9. Use according to one of claims 1 to 8, wherein n is 1.

10. Use according to one of claims 1 to 9, wherein the configuration of the substituents R_2, R_3, R_4 and $R_5OOCPO(OH)OCH_2$ is D-gluco.

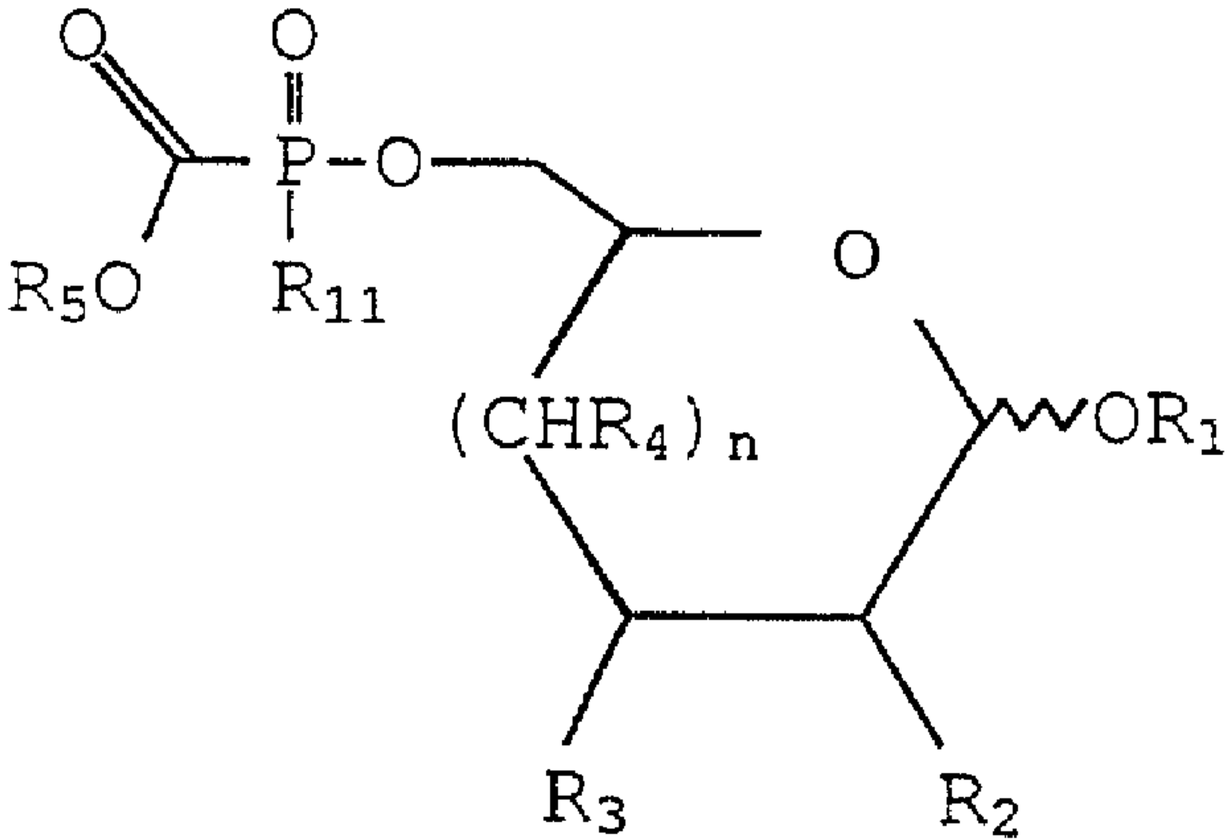
11. Use according to one of the preceding claims for the treatment of infections caused by bacteria, fungi or uni- or multicellular parasites.

12. Use according to claim 11 for the treatment of infections which are caused by bacteria which are selected from the group which consists of bacteria of the family Propionibacteriaceae, in particular of the genus Propionibacterium, in particular the species Propionibacterium acnes, bacteria of the family Actinomycetaceae, in particular of the genus Actinomyces, bacteria of the genus Cornynebacterium, in particular the species Corynebacterium diphtheriae and Corynebacterium pseudotuberculosis, bacteria of the family Mycobacteriaceae, of the genus Mycobacterium, in particular the species Mycobacterium leprae, Mycobacterium tuberculosis, Mycobacterium bovis and Mycobacterium avium, bacteria of the family Chlamydiaceae, in particular the species Chlamydia trachomatis and Chlamydia psittaci, bacteria of the genus Listeria, in particular the species Listeria monocytogenes, bacteria of the species Erysipelthrix rhusiopathiae, bacteria of the genus Clostridium, bacteria of the genus Yersinia, the species Yersinia pestis, Yersinia pseudotuberculosis, Yersinia enterocolitica and Yersinia ruckeri, bacteria of the family Mycoplasmataceae, of the genera Mycoplasma and Ureaplasma, in particular the species Mycoplasma pneumoniae, bacteria of the genus Brucella, bacteria of the genus Bordetella, bacteria of the family Neisseriaceae, in particular of the genera Neisseria and Moraxella, in particular the species Neisseria meningitides, Neisseria gonorrhoeae and Moraxella bovis, bacteria of the family Vibrionaceae, in particular of the genera

Vibrio, Aeromonas, Plesiomonas and Photobacterium, in particular the species Vibrio cholerae, Vibrio anguillarum and Aeromonas salmonicidas, bacteria of the genus Campylobacter, in particular the species Campylobacter jejuni, Campylobacter coli and Campylobacter fetus, bacteria of the genus Helicobacter, in particular the species Helicobacter pylori, bacteria of the families Spirochaetaceae and Leptospiraceae, in particular of the genera Treponema, Borrelia and Leptospira, in particular Borrelia burgdorferi, bacteria of the genus Actinobacillus, bacteria of the family Legionellaceae, of the genus Legionella, bacteria of the family Rickettsiaceae and family Bartonellaceae, bacteria of the genera Nocardia and Rhodococcus, bacteria of the genus Dermatophilus, bacteria of the family Pseudomonadaceae, in particular of the genera Pseudomonas and Xanthomonas, bacteria of the family Enterobacteriaceae, in particular of the genera Escherichia, Klebsiella, Proteus, Providencia, Salmonella, Serratia and Shigella, bacteria of the family Pasteurellaceae, in particular of the genus Haemophilus, bacteria of the family Micrococcaceae, in particular of the genera Micrococcus and Staphylococcus, bacteria of the family Streptococcaceae, in particular of the genera Streptococcus and Enterococcus and bacteria of the family Bacillaceae, in particular of the genera Bacillus and Clostridium, and in the eradication of Helicobacter in ulcers of the gastrointestinal tract.

13. Use according to claim 11 for the prevention and treatment of infections caused by unicellular parasites which are selected from the group which consists of the causative organisms of malaria, sleeping sickness, Chagas' disease, toxoplasmosis, amoebic dysentery, leishmaniases, trichomoniasis, pneumocystosis, balantidiasis, cryptosporidiosis, sarcocytosis, acanthamoebosis, naeglerosis, coccidiosis, giardiasis and lambliasis.

14. Process for the treatment of infectious diseases caused by bacteria, fungi or parasites in which a therapeutically effective quantity of a compound according to one of claims 1 to 11 is administered to a patient suffering from an infection caused by bacteria, fungi or parasites.



(I)