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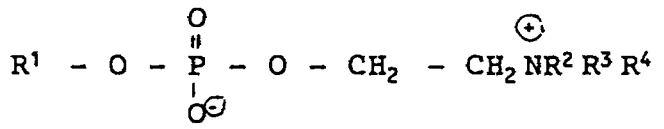
Process for the production of a pharmaceutical agent for oral or topical administration in the treatment of leishmaniasis

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C l a i m s

1. Process for the production of a pharmaceutical agent for oral or topical administration in the treatment of protozoal diseases, in particular of leishmaniasis, which contains as the active substance one or several compounds having the general formula I



(I)

in which R^1 is a saturated or monounsaturated or polyunsaturated hydrocarbon residue with 12 to 20 C atoms and R^2, R^3 and R^4 denote independently of one another hydrogen, a C_1-C_5 alkyl group, a C_3-C_6 cycloalkyl group or a C_1-C_5 hydroxyalkyl group whereby two of the residues R^2, R^3 and R^4 can together form a C_2-C_5 alkylene group which, if desired, can be substituted with an -O-, -S- or NR^5 group, in which R^5 is hydrogen, a C_1-C_5 alkyl group, a C_3-C_6 cycloalkyl group or a C_1-C_5 hydroxyalkyl group as well as, if desired the usual pharmaceutical auxiliary, diluting, carrier or/and filling substances.

2. Process as claimed in claim 1,
w h e r e i n
R^1 is straight-chained and has 16 to 20 C atoms.

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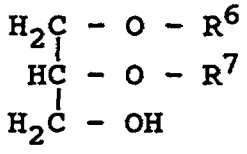
3. Process as claimed in claim 1,
w h e r e i n
the residues R^2, R^3 and R^4 are independently of each other methyl, ethyl, hydroxyethyl or C_3-C_6 cycloalkyl residues.

4. Process as claimed in claim 3,
w h e r e i n
R^2, R^3 and R^4 are methyl residues.

5. Process as claimed in one of the previous claims,
w h e r e i n
R^1 is a hexadecyl, octadecyl, oleyl, elaidyl, eicosyl or eicosenyl-cis(ω-9) residue.

6. Process as claimed in claim 5,
w h e r e i n
R^1 is a hexadecyl or octadecyl residue.

7. Process as claimed in one of the previous claims,
w h e r e i n
the pharmaceutical agent additionally contains one or several alkyl glycerols having the general formula II



(II)

in which one of the residues R^6 and R^7 denotes an alkyl group with 2 to 12 C atoms and the other residue denotes a hydrogen atom.

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8. Process as claimed in claim 7,
w h e r e i n
the pharmaceutical agent contains an alkyl glycerol mixture of nonyl or octyl glycerol, hexyl or pentyl glycerol and propyl or ethyl glycerol as well as, if desired, water.

9. Process as claimed in one of the previous claims,
w h e r e i n
the pharmaceutical agent contains 5 to 2000 mg, in particular 10 to 500 mg, of one or several compounds having the general formula I in one dosage unit.

10. Process as claimed in one of the previous claims,
w h e r e i n
it contains as a topical pharmaceutical agent 5 - 200 mg of one or several compounds having the general formula I per ml of an alkyl glycerol having the formula II or of a corresponding alkyl glycerol mixture.

11. Process as claimed in one of the claims 1 to 10,
w h e r e i n
it is formulated as a drinking solution having a daily dose between 1 and 10 mg/kg of one or several compounds having the general formula I.

12. Process as claimed in one of the claims 1 to 10,
w h e r e i n
one or several compounds having the general formula I are mixed or homogenized with the usual physiologically tolerated filling, carrier, dilution or/and auxiliary substances at

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temperatures between 20 and 120°C and, if desired, in order to prepare formulations which contain 10 to 800 mg of compounds having the general formula I in one dosage unit, the mixture thus obtained is poured into hollow cells of an appropriate size or filled into capsules of an appropriate size or granulated and then pressed into tablets, if desired, with addition of further common auxiliary substances.

13. Process as claimed in claim 12,
w h e r e i n
one or several compounds having the general formula I are mixed with one or several of the following auxiliary substances: starch, cellulose, lactose, formalin-casein, modified starch, magnesium stearate, calcium hydrogenphosphate, highly-dispersed silicic acid, talcum and phenoxyethanol, the mixture obtained is granulated if desired with an aqueous solution containing the constituents gelatin, starch, polyvinyl pyrrolidone, vinylpyrrolidone-vinyl acetate copolymerisate or/and polyoxyethylene sobitanmonooleate, the granulate is homogenized, if desired, with one or several of the aforementioned auxiliary substances and this mixture is pressed into tablets or filled into capsules whereby the tablets or capsules each contain 10 to 800 mg of compounds having the general formula I in one dosage unit.

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14. Process as claimed in one of the claims 12 or 13, w h e r e i n
one or several compounds having the general formula I are suspended with soybean lecithin as well as if desired, 0.1 to 0.5 parts by weight phenoxyethanol (in relation to one part by weight of compounds having the general formula I) at temperatures between 33 - 37°C in melted resin fat and homogenized and subsequently the mixture is poured into hollow cells whereby the dosage unit contains 10 to 800 mg of compounds having the formula I.

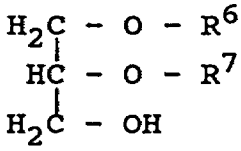
15. Process as claimed in one of the claims 12 or 13, w h e r e i n,
one or several compounds having the general formula I are homogenized at a temperature between 50 and 120°C, if desired, in the presence of one or several emulsifiers or/and 0.1 - 0.5 parts by weight phenoxyethanol (in relation to 1 part by weight of compounds having the formula I) with at least one of the following substances: paraffin, vaseline, aliphatic alcohols with 12 to 25 C atoms, sorbitanmonopalmitate, aliphatic monocarboxylic acid with 15 to 20 C atoms, polyoxyethylene polyol fatty acid ester, and the homogenized mixture is emulsified, if desired, with addition of a multivalent lower aliphatic alcohol.

16. Process as claimed in one of the claims 12 to 15, w h e r e i n
one or several compounds having the general formula I are dissolved at temperatures between 30 - 100°C, if desired, in the presence of 0.1 - 0.5 parts by weight phenoxyethanol (in relation to one part by weight of compounds having the formula I) as well

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as, if desired, in the presence of an emulsifier and if desired, the solution thus obtained is filled up with sufficient water or vegetable oil so that the final solution contains 0.1 - 5 percent by weight of compounds having the formula I.

17. Process as claimed in one of the claims 7 to 16, w h e r e i n an alkyl glycerol is additionally used in the production having the formula II



(II)

in which one of the residues R^6 and R^7 denotes an alkyl group with 2 to 12 C atoms and the other residue denotes a hydrogen atom, or a mixture of such alkyl glycerols as well as, if desired, water is used whereby 1 - 30 parts by weight of an alkyl glycerol having the formula II or of a corresponding alkyl glycerol mixture and if desired 1 - 30 parts by weight of water, each in relation to 1 part by weight of compounds having the formula I, are used.

18. Use of one or several compounds having the general formula I defined in claim 1 for the treatment of protozoal diseases, in particular of leishmaniasis.

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19. Use as claimed in claim 18,
w h e r e i n
the agent additionally contains one or several alkyl glycerols having the general formula II defined in claim 7.

20. Process for the treatment of protozoal diseases, in particular of leishmaniasis,
w h e r e i n
a pharmaceutical agent as claimed in one of the claims 1 to 17 is administered topically or orally.

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Description

The present invention concerns a process for the production of a pharmaceutical agent for oral or topical administration in the treatment of protozoal diseases, in particular of leishmaniasis.

Leishmaniasis is a name for various tropical diseases which are caused by flagellates of the genus Leishmania and is transmitted by various blood-sucking insects. The manifestations of leishmaniasis may be visceral (kala-azar), mucocutaneous (american leishmaniasis) or cutaneous (Aleppo boil or diffuse cutaneous leishmaniasis). The incubation period is weeks or months. A very high mortality rate is observed in untreated cases, in particular with kala-azar and american leishmaniasis.

The therapeutic agents used today for the treatment of leishmaniasis are pentavalent antimony compounds (e.g. sodium stibogluconate) and aromatic diamidines. A disadvantage of these drugs is, however, that they cause severe side-effects such as nausea and vomitting due to their high toxicity. Moreover there are already Leishmania strains which are resistant to antimony.

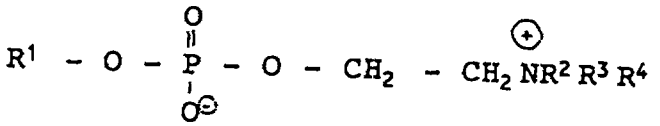
Croft et al (Biochem. Pharmacol. 36 (1987), p. 2633-2636) describe experiments in which the effectiveness of alkyl phosphocholines against Leishmania donovani was investigated. The effect of alkyl phosphocholines was tested in comparison with the effect of the standard therapeutic preparation, sodium stibogluconate, (Pentostam) when administered subcutaneously. In this process it was found that alkyl phosphocholines, in

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particular C_{22} alkyl phosphocholines are active against Leishmania. It was, however, also established that the alkyl phosphocholines, in particular hexadecyl-phosphocholine, were highly toxic for the experimental animals, in particular for macrophages in therapeutically effective doses so that they do not represent a real alternative when administered subcutaneously to the known therapy with sodium stibogluconate.

Thus the object of the present invention was to provide a pharmaceutical agent for protozoal diseases, in particular for leishmaniasis, in which the disadvantages of the state of the art, in particular with regard to the severe side-effects, are at least partially eliminated.

The object according to the present invention is achieved by a process for the production of a pharmaceutical agent for oral or topical administration in the treatment of protozoal diseases, in particular of leishmaniasis, which contains as the active substance one or several compounds having the general formula I



(I)

in which R^1 is a saturated or monounsaturated or polyunsaturated hydrocarbon residue with 12 to 20 C atoms and R^2, R^3 and R^4 denote independently of one another hydrogen, a C_1-C_5 alkyl group, a C_3-C_6

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cycloalkyl group or a C_1-C_5 hydroxyalkyl group whereby two of the residues R^2, R^3 and R^4 can together form a C_2-C_5 alkylene group which, if desired, can be substituted with an -O-, -S- or NR^5 group, in which R^5 is hydrogen, a C_1-C_5 alkyl group, a C_3-C_6 cycloalkyl group or a C_1-C_5 hydroxyalkyl group as well as, if desired the usual pharmaceutical auxiliary, diluting, carrier or/and filling substances.

In the general formula I, R^1 can be branched or straight-chained. R^1 is preferably a straight-chained hydrocarbon residue with 16 to 20 C atoms, in particular a hexadecyl, octadecyl, oleyl, elaidyl, eicosyl or eicosenyl-cis-(ω-9) residue. R^1 is particularly preferably a hexadecyl or octadecyl residue.

Examples of suitable residues R^2, R^3 and R^4 in the formula I are for instance methyl, ethyl, propyl, butyl and pentyl residues, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl residues, hydroxymethyl, hydroxyethyl and hydroxypropyl residues. Two of the residues R^2, R^3 and R^4 can for example form a pyrrolidine, a piperidine or a morpholine group. At least one of the residues R^2, R^3 and R^4 is preferably different from hydrogen, it is particularly preferred that all 3 residues are different from hydrogen.

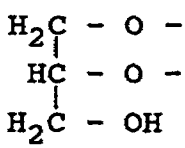
Examples of preferred residues R^2, R^3 and R^4 are methyl, ethyl, hydroxyethyl and C_3-C_6 cycloalkyl residues. If one of R^2, R^3 and R^4 is a cycloalkyl residue, then the other two residues are preferably methyl residues. It is particularly preferred that the residues R^2, R^3 and R^4 are independently of each other methyl or ethyl residues. It is most preferred when R^2, R^3 and R^4 are methyl residues so that alkyl phosphocholines represent

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a particularly preferred class of compounds which is suitable for the production of an agent against protozoal diseases, in particular against leishmaniasis.

It was surprisingly found that compounds having the general formula I when administered orally or topically show no measurable side-effects and a very much higher activity than sodium stibogluconate. In any case the therapeutic agents according to the present invention constitute the first forms of oral therapy for leishmaniasis diseases, and they are considerably more effective than Pentostam, a standard therapeutic preparation used worldwide in the liver and in particular also in the spleen.

In a preferred embodiment of the present invention the oral or topical therapeutic preparation additionally contains one or several alkyl glycerols having the general formula II



(II)

in which one of the residues R^6 and R^7 denotes an alkyl group with 2 to 12 C atoms and the other residue denotes a hydrogen atom. An alkyl glycerol mixture is preferably used which contains nonyl or octyl glycerol, hexyl or pentyl glycerol and propyl or ethyl glycerol as well as, if desired, water.

The pharmaceutical agent according to the present invention contains in one dosage unit preferably 5 to 2000 mg, particularly preferably 10 to 500 mg of one or

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several compounds having the general formula I. For topical administration the pharmaceutical agent according to the present invention preferably contains 5 to 200 mg of one or several compounds having the general formula I per ml of an alkyl glycerol having the formula II or of a corresponding alkyl glycerol mixture.

For oral administration the pharmaceutical agent according to the present invention is preferably formulated as a drinking solution with a daily dosage between 1 and 10 mg/kg of one or several compounds having the general formula I.

The production of an oral pharmaceutical agent according to the present invention can on the other hand also be carried out by mixing or homogenizing one or several compounds having the general formula I with the usual physiologically tolerated filling, carrier, dilution or/and auxiliary substances at temperatures between 20 and 120°C and, if desired in order to prepare formulations which contain 10 to 800 mg of compounds having the general formula I in one dosage unit, the mixture thus obtained is poured into hollow cells of an appropriate size or filled into capsules of an appropriate size or granulated and then pressed into tablets, if desired, with addition of further common auxiliary substances. The active substance can for example be mixed with one or several of the following auxiliary substances: starch, cellulose, lactose, formalin-casein, modified starch, magnesium stearate, calcium hydrogenphosphate, highly-dispersed silicic acid, talcum and phenoxyethanol. The mixture obtained is granulated, if desired, with an aqueous solution containing for example gelatin, starch, polyvinyl pyrrolidone, vinylpyrrolidon-vinyl acetate

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copolymerisate or/and polyoxyethylene sobitanmonooleate, as constituent and the granulate is homogenized, if desired, with one or several of the aforementioned auxiliary substances. Subsequently this mixture can be pressed into tablets or filled into capsules whereby the tablets or capsules each contain 10 to 800 mg of active substance in one dosage unit.

In a particularly preferred embodiment the active substance is suspended with soybean lecithin as well as, if desired, 0.1 to 0.5 parts by weight phenoxyethanol (in relation to one part by weight of the active substance) at temperatures between 33 and 37°C in melted resin fat and homogenized and subsequently the mixture is poured into hollow cells whereby one dosage unit contains 10 to 800 mg of the active substance.

Moreover the active substance can be homogenized at a temperature between 50 and 120°C, if desired in the presence of one or several emulsifiers or/and 0.1 - 0.5 parts by weight phenoxyethanol (in relation to 1 part by weight of the active substance) with at least one of the following substances: paraffin, vaseline, aliphatic alcohol with 12 to 25 C atoms, sorbitanmonopalmitate, aliphatic monocarboxylic acid with 15 to 20 C atoms, polyoxyethylenepolyol fatty acid ester. If desired, the mixture obtained can be emulsified with addition of a multivalent lower (preferably C_2-C_3) aliphatic alcohol (e.g. ethylene glycol, diethylene glycol, propylene glycol, dipropylene glycol and in particular glycerol).

On the other hand, if desired, the active substance can be dissolved at temperatures between 30 and 100°C in the presence of 0.1 - 0.5 parts by weight phenoxyethanol (in relation to one part by weight of the active substance)

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as well as, if desired, in the presence of an emulsifier and if desired the solution thus obtained is filled up with sufficient water or vegetable oil so that the final solution contains 0.1 to 5 % by weight of the active substance.

The active substance can also be mixed together with an alkyl glycerol having the general formula II or with a mixture of such alkyl glycerols as well as, if desired, water in which 1 to 30 parts by weight alkyl glycerol having the general formula II or of a corresponding alkyl mixture and if desired 1 to 30 parts by weight water, each in relation to 1 part by weight active substance according to general formula I, are used.

The present invention also concerns the use of one or several compounds having the general formula I as the active substance for an oral or a topical agent for treating protozoal diseases, in particular leishmaniasis. In this connection the agent can additionally contain one or several alkyl glycerols having the general formula II, in particular for topical applications.

Finally the invention also concerns a process for the treatment of protozoal diseases, in particular of leishmaniasis, which is characterized in that a pharmaceutical agent produced according to the present invention is administered topically or orally.

The production of compounds having the general formula I is described in detail in the examples for hexadecyl-phosphocholine. Further methods for the production of compounds having the general formula I are described for

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example in DE-A 27 52 125, DE-A 36 41 379, DE-A 36 41 491, DE-A 40 13 632, DE-A 36 41 377, the literature cited in these or in earlier patent applications or patent specifications of the same applicant. Reference is expressly made to this literature for the present patent application.

The pharmaceutical agents according to the present invention are preferably used for the treatment of leishmaniasis. Other protozoal diseases which can be treated by the agent according to the present invention are for instance malaria, trypanosomiasis, toxoplasmosis, babesiosis, amoebic dysentery and lambliasis. The agents according to the present invention are in particular suitable for those diseases in which the pathogen is present in organs such as the liver, spleen or kidney.

It is intended to elucidate the invention further by the following examples.

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Example 1

Production of hexadecylphosphocholine·H_2O

a) Hexadecylphosphoethanolamine
(phosphorylation, ring closure and ring opening)

Hexadecanol (1 mole, 243 g) and triethylamine (1.8 mole, 180 g) are dissolved in 1.5 l THF (tetrahydrofuran) and added dropwise to a solution of phosphoroxychloride (1.2 mole, 184 g) in 120 ml THF which was stirred vigorously in such a way that the temperature in the reaction vessel (three-neck, 5 l, with dropping funnel, thermometer and stirrer) does not exceed 10°C. In order to accelerate the process, the reaction vessel is cooled with an ice-salt mixture. The reaction is completed immediatly after the dropwise addition (detected by TLC in ether: Rf values of 0.8 for the initial product, of 0.0 for the reaction product after hydrolysis with water).

The ice-bath is removed and a solution of ethanolamine (1.5 mole, 92 g) and triethylamine (1.8 mole, 180 g) in 1 l dioxan are added while stirring vigorously in such a way that the temperature in the reaction vessel increases to 65 to 70°C. Then the ring formation is completed (detected by TLC in ether: Rf values of 0.2). Precipitated triethylamine hydrochloride is removed by filtration while still warm and 1.5 l 2N formic acid is added to the filtrate at 40 to 50°C. After 15 minutes the ring opening is completed (detected by TLC in ether: Rf values 0.0; TLC in chloroform/methanol/acetic acid/water 100:60:20:5 by volume: Rf value 0.8). It is cooled to -20°C and the precipitate which is mainly composed of pure hexadecylphosphoethanolamine is filtered off. If slight impurities are present a subsequent chromatographic purification is carried out.

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Microanalysis (MW 365.50):				
calc. (%)	C 59.15	H 11.03	N 3.83	P 8.48
found (%)	59.01	10.95	3.79	8.31

Methylation of hexadecylphosphoethanolamine

The crystals obtained according to example 1 are taken up in 1.2 l 2-propanol and 0.4 l dichloromethane without further purification. Potassium carbonate (4 mole, 560 g) is added to the suspension of the crystals in 1 l water while stirring vigorously. Dimethyl sulfate (4 mole, 500 g) is added dropwise to the two-phase reaction mixture while stirring in such a way that the temperature does not exceed 40°C. The reaction is completed 60 minutes after the dropwise addition (detected by TLC in chloroform/methanol/25 % ammonia 50:50:5 by volume: Rf value 0.3). After phase separation at 20°C, the upper phase contains the product. The solvent is removed in a rotary evaporator under a vacuum and the viscous residue is chromatographed on silica gel (Merck product No. 7733, silica gel 60, particle size 0.2 to 0.5 mm).

Chromatography

Chloroform/methanol/25 % ammonia (200/15/1 by volume) is added to 2 kg silica gel and filled into a chromatography column. The viscous oil is dissolved in 800 ml of the above solvent mixture and the crude product is applied to the column (insoluble components are previously removed by filtration). It is eluted with mobile solvents of increasing polarity until the impurities are washed out. The product is finally eluted with chloroform/methanol/25 % ammonia (50/50/5 by

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volume). The combined eluates are rotary evaporated and the remaining water is removed with toluol. The residue is taken up in 600 ml dichloromethane and 4 l acetone is added. The crystals which separate out at -20°C are washed with cold acetone, then with pentane and dried in a vacuum. The yield of pure hexadecylphospocholine is 250 g (ca. 70 % in relation to hexadecylglycerol).
Microanalysis (MW 407.58):

calc. (%):	C 59.27	H 11.37	N 3.29	P 7.28
found (%):	58.98	11.31	3.21	7.11

Production of pharmaceutical formulations

Example for a solution:
25 g 1-n-propyloxy-2,3-propanediol, 12.5 g 1-n-hexyloxy-2,3-propanediol, 12.5 g 1-n-nonyloxy-2,3-propanediol, 44 g water and 1 g phenoxyethanol are mixed and 5 g hexadecylphosphocholine is dissolved in this mixture. The solution is freed of visible particles by filtration over suitable filters.
1 g solution contains 50 mg hexadecylphosphocholine.

Example for a an ointment:
5 g hexadecylphosphocholine is suspended in 35 g viscous paraffin, 30 g emulsified cetylstearyl alcohol and 30 g white vaseline are added and melted. This melt is first stirred until it has cooled down. A homogeneous distribution of active substance is achieved by processing the cooled melt by means of a suitable homogenizer (e.g. three-roll mill).
1 g of the hydrophilic ointment contains 50 mg hexadecylphosphocholine.

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Example for an emulsion:
11.83 g 1-n-propyloxy-2,3-propanediol, 5.91 g 1-n-hexaloxy-2,3-propanediol, 5.91 g 1-n-nonyloxy-2,3-propanediol, 20.35 g water and 1.0 g phenoxyethanol are mixed and 5 g hexadecylphosphocholine is dissolved in this mixture. 30 g white vaseline, 15 g cetylalcohol and 5 g sorbitan monopalmitate are melted on a water-bath, heated to 70°C and the solution of the active substance, which was also heated to 70°C, is emulsified in the fat phase with the aid of a high-speed dispersing apparatus. The cream is subsequently cooled down to 30°C while stirring. 1 g water-in-oil cream contains 50 mg hexadecylphosphocholine.

Example for capsules:
1.25 kg hexadecylphospocholine is dissolved in 5 kg chloroform and 1.25 kg aerosil is suspended in this solution. The solvent is subsequently removed in a vacuum. The dry mass is passed through a 1 mm sieve and dried once again in a vacuum at 30°C in order to remove any last remains of solvent. This granulate is filled in a known way to 500 mg into gelatin hard capsules with a size of 00 using a suitable capsule machine.
One capsule contains 250 mg hexadecylphosphocholine.

Examples of further active substances

Example 2
Octadecylphosphocholine
$C_{23}H_{50}NO_4P$ MW 435.630

Example 3
Oleylphosphocholine
$C_{23}H_{48}NO_4P$ MW 433.614

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Example 4
Elaidylphosphocholine
$C_{23}H_{48}NO_4P$ MW 433.614

Example 5
Hexadecylphospho-(N.N-dimethyl-N-ethyl)ethanolamine MW 421.603

Example 6
Octadecylphospho-(N.N-dimethyl-N-ethyl)ethanolamine MW 449.657

Example 7
Oleylphospho-(N.N-dimethyl-N-ethyl)ethanolamine MW 447.641

Example 8
Elaidylphospho-(N.N-dimethyl-N-ethyl)ethanolamine MW 447.641

Example 9
Hexadecylphospho-(N-cyclopropyl-N.N-dimethyl)-ethanolamine
$C_{23}H_{48}NO_4P$ MW 443.614

Example 10
Hexadecylphospho-(N-cyclobutyl-N.N-dimethyl)-ethanolamine
$C_{24}H_{50}NO_4P$ MW 447.641

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Example 11

Hexadecylphospho-(N-cyclopentyl-N.N-dimethyl)-ethanolamine

$C_{25}H_{52}NO_4P$ MW 461.668

Example 12

Hexadecylphospho-(N.N-dimethyl-N-hydroxyethyl)-ethanolamine

$C_{22}H_{48}NO_5P$ MW 437.602

Example 13

Hexadecylphospho-(N-methyl)-pyrrolidino-ethyl ester

$C_{23}H_{48}NO_4P$ MW 433.614

Example 14

Octadecylphospho-(N.N-diethyl-N-methyl)-ethanolamine

$C_{25}H_{54}NO_4P$ MW 463.684

Example 15

Octadecylphospho-(N-cyclopropyl-N.N-dimethyl)-ethanolamine

$C_{25}H_{52}NO_4P$ MW 461.668

Example 16

Octadecylphospho-(N-cyclobutyl-N.N-dimethyl)-ethanolamine

$C_{26}H_{54}NO_4P$ MW 475.695

Example 17

Octadecylphospho-(N-cyclopentyl-N.N-dimethyl)-ethanolamine

$C_{27}H_{56}NO_4P$ MW 489.722

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Example 18

Octadecylphospho-(N.N-dimethyl-N-hydroxyethyl)-ethanolamine

$C_{24}H_{52}NO_4P$ MW 465.656

Example 19

Octadecylphospho-(N-methyl)-pyrrolidino-ethyl ester

$C_{25}H_{52}NO_4P$ MW 461.668

Example 20

Oleylphospho-(N.N-diethyl-N-methyl)-ethanolamine

$C_{25}H_{52}NO_4P$ MW 461.668

Example 21

Oleylphospho-(N-cyclopropyl-N.N-dimethyl)-ethanolamine

$C_{25}H_{50}NO_4P$ MW 459.652

Example 22

Oleylphospho-(N-cyclopentyl-N.N-dimethyl)-ethanolamine

$C_{27}H_{54}NO_4P$ MW 487.706

Example 23

Oleylphospho-(n.N-dimethyl-N-hydroxyethyl)-ethanolamine

$C_{24}H_{50}NO_5P$ MW 463.640

Example 24

Oleylphospho-(N-methyl)-pyrrolidino-ethyl ester

$C_{25}H_{50}NO_4P$ MW 459.652

Example 25

Elaidylphospho-(N-cyclopropyl-N.N-dimethyl)-ethanolamine

$C_{25}H_{50}NO_4P$ MW 459.652

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Example 26
Elaidylphospho-(N.N-dimethyl-N-hydroxyethyl)-ethanolamine
$C_{24}H_{50}NO_5P$ MW 463.640

Example 27
Elaidylphospho-(N-methyl)-pyrrolidino-ethyl ester
$C_{25}H_{50}NO_4P$ MW 459.652

Example 28
Eicosylphosphocholine
$C_{25}H_{54}NO_4P$ MW 463.684

Example 29
Eicosylphospho-(N-ethyl-N.N-dimethyl)-ethanolamine
$C_{26}H_{56}NO_4P$ MW 477.711

Example 30
Eicosylphospho-(N.N-diethyl-N-methyl)-ethanolamine
$C_{27}H_{54}NO_4P$ MW 491.738

Example 31
Eicosylphospho-(N-cyclopropyl-N.N-dimethyl)-ethanolamine
$C_{27}H_{56}NO_4P$ MW 489.722

Example 32
Eicosylphospho-(N.N-dimethyl-N-hydroxyethyl)-ethanolamine
$C_{26}H_{56}NO_5P$ MW 493.710

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Example 33
Eicosylphospho-(N.N-dihydroxyethyl-N-methyl)-ethanolamine
$C_{27}H_{58}NO_6P$ MW 523.736

Example 34
Eicosylphospho-(N-methyl)-pyrrolidino-ethyl ester
$C_{27}H_{56}NO_4P$ MW 489.722

Example 35
Eicosenyl-cis-(ω-9)-phosphocholine
$C_{25}H_{52}NO_4P$ MW 461.668

Example 36
Eicosenyl-cis-(ω-9)-phospho-(N-ethyl-N.N-dimethyl)-ethanolamine
$C_{26}H_{54}NO_4P$ MW 475.695

Example 37
Eicosenyl-cis-(ω-9)-phospho-(N-cyclopropyl-N.N-dimethyl)-ethanolamine
$C_{27}H_{54}NO_4P$ MW 487.706

Example 38
Eicosenyl-cis-(ω-9)-phospho-(N.N-dimethyl-N-hydroxyethyl)-ethanolamine
$C_{26}H_{54}NO_5P$ MW 491.694

Example 39
Effect of various leishmaniasis drugs on the presence of pathogens in the liver of experimental animals (rats) infected with L. donovani.

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The effect of the phospholipids according to the present invention (hexadecylphosphocholine, octadecylphosphocholine and oleylphospho-(N.N-dimethyl-N-ethyl)-ethanolamine) was compared with the standard therapeutic agent Pentostam used worldwide and the ether lipid $Et_{18}OCH_3$ (1-octadecyl-2-methyl-rac-glycero-3-phosphocholine).

The compounds according to the present invention and $Et_{18}OCH_3$ were administered orally while Pentostam was administered intravenously. It was found that the alkyl phosphocholines with a C_{18} and C_{16} chain were 32-times more effective than the standard therapeutic agent Pentostam while olely-phospho-(N.N-dimethyl-N-ethyl)ethanolamine has a comparable effect to Pentostam.

The results of this experiment are shown in Table 1. The number of pathogens per liver was determined by microscopic analysis.

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Table 1
Number of leishmania pathogens in the liver after a 3 week period of therapy

	Pathogens per liver (in millions)	Relative effectiveness (pathogens per liver after Pentostam therapy divided by pathogens/liver after addition of test substance
Control	536.9	---
1-octadecyl-2-methyl-rac-glycero-3-phospho-choline[1]	424.7	0.007
Oleylphospho-(N.N-dimethyl-N-ethyl)-ethanolamine[1]	4.7	0.7
Pentostam[2]	3.2	1.0
Hexadecylphospho-choline[1]	0.1	32.0
Octadecylphospho-choline[1]	0.1	32.0

[1] Alkyl-PC and $Et_{18}OCH_3$ - orally: 5 x 20 mg/kg/week for 3 weeks
[2] Pentostam - iv.: 5 x 120 mg/kg/week for 3 weeks

In some additional experiments parasites were no longer microscopically detectable in the liver and in the spleen after single oral dose of 200 mg hexadecylphosphocholine.

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Example 40

Effect of different leishmaniasis drugs on the presence of pathogens in the spleen

The experimental procedure was as described in example 39. The results of these experiments are shown in Table II.

Table II

Number of leishmania pathogens in the spleen after a 3 week period of therapy

	Pathogens per spleen (in millions)	Relative effectiveness (pathogens per spleen afte Pentostam therapy divided by pathogens/spleen after addition of test substance
Control	24.3	---
1-octadecyl-2-methyl-rac-glycero-3-phospho-choline	6.5	0.9
Oleylphospho-(N.N-dimethyl-N-ethyl)-ethanolamine[1]	0.03	210.0
Pentostam	6.3	1.0
Hexadecylphospho-choline	0.01	630.0
Octadecylphospho-choline	0.01	630.0

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The weak effect of Pentostam in the spleen is surprising. The alkylphosphocholines are in this case > 600-fold more effective than the standard therapy.

In several additional experiments parasites were no longer microscopically detectable after a single oral dose of 200 mg hexadecylphosphocholine.

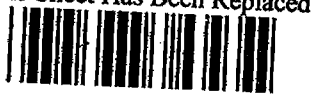
Table III shows the concentration of hexadecyl-phosphocholine (C_{16}-O-PC), octadecylphosphocholine (C_{18}-O-PC) and 1-octadecyl-2-methyl-rac-glycero-3-phosphocholine ($Et_{18}OCH_3$) in the organs of the rat after oral administration of 50 µmol/day for 5 days, a pause of 2 days then for a further 4 days at 50 µmol/day.

Table III

Organ	Amount of substance (nmol/g fresh tissue)		
	C_{16}-O-PC	C_{18}-O-PC	$Et_{18}OCH_3$
Serum	130	47	5
Liver	272	298	36
Spleen	410	424	43
Kidney	853	406	57

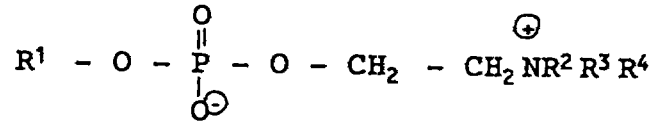
It is surprising how well hexadecylphosphocholine and octadecylphosphocholine accumulate in the spleen. It is especially in the spleen that the standard therapeutic agent Pentostam has an extremely low effectiveness. In comparison to this $Et_{18}OCH_3$ is only present in the spleen and in the liver in extremely low concentrations.

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A b s t r a c t

The invention concerns a new pharmaceutical agent for oral or topical administration in the treatment of protozoal diseases, in particular of leishmaniasis, which contains as the active substance one or several compounds having the general formula I



(I)

in which R^1 is a saturated or monounsaturated or polyunsaturated hydrocarbon residue with 12 to 20 C atoms and R^2, R^3 and R^4 denote independently of one another hydrogen, a C_1-C_5 alkyl group, a C_3-C_6 cycloalkyl group or a C_1-C_5 hydroxyalkyl group whereby two of the residues R^2, R^3 and R^4 can together form a C_2-C_5 alkylene group which, if desired, can be substituted with an -O-, -S- or NR^5 group, in which R^5 is hydrogen, a C_1-C_5 alkyl group, a C_3-C_6 cycloalkyl group or a C_1-C_5 hydroxyalkyl group as well as, if desired the usual pharmaceutical auxiliary, diluting, carrier or/and filling substances.

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☑ Description : paged 2,3,5,7,8 to paged ...
☑ Claim(s) : paged 22 to paged 28
☐ Drawing(s) : paged ..... to paged .....
☐ Abstract : paged ..... to paged .....
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☑ Description : paged 1 to paged 2
☑ Claim(s) : paged 22 to paged 28
☐ Drawing(s) : paged ..... to paged ...
☑ Abstract : paged 29 to paged ...
DATE OF RECEIPT 7/10/96

PROCESS FOR THE PRODUCTION OF A PHARMACEUTICAL AGENT FOR ORAL OR TOPICAL ADMINISTRATION IN THE TREATMENT OF LEISHMANIASIS

Description

The present invention concerns a process for the production of a pharmaceutical agent for oral or topical administration in the treatment of protozoal diseases, in particular of leishmaniasis.

Leishmaniasis is a name for various tropical diseases which are caused by flagellates of the genus Leishmania and is transmitted by various blood-sucking insects. The manifestations of leishmaniasis may be visceral (kala-azar), mucocutaneous (american leishmaniasis) or cutaneous (Aleppo boil or diffuse cutaneous leishmaniasis). The incubation period is weeks or months. A very high mortality rate is observed in untreated cases, in particular with kala-azar and american leishmaniasis.

The therapeutic agents used today for the treatment of leishmaniasis are pentavalent antimony compounds (e.g. sodium stibogluconate) and aromatic diamidines. A disadvantage of these drugs is, however, that they cause severe side-effects such as nausea and vomitting due to their high toxicity. Moreover there are already Leishmania strains which are resistant to antimony.

Croft et al (Biochem. Pharmacol. 36 (1987), p. 2633-2636) describe experiments in which the effectiveness of alkyl phosphocholines against Leishmania donovani was investigated. The effect of alkyl phosphocholines was tested in comparison with the effect of the standard therapeutic preparation, sodium stibogluconate, (Pentostam) when administered subcutaneously. In this process it was found that alkyl phosphocholines, in

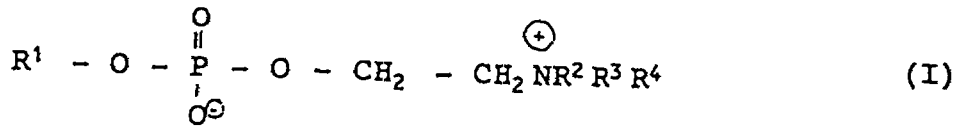
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particular C_{22} alkyl phosphocholines are active against Leishmania. It was, however, also established that the alkyl phosphocholines, in particular hexadecyl-phosphocholine, were highly toxic for the experimental animals, in particular for macrophages in therapeutically effective doses so that they do not represent a real alternative when administered subcutaneously to the known therapy with sodium stibogluconate.

Thus the object of the present invention was to provide a pharmaceutical agent for protozoal diseases, in particular for leishmaniasis, in which the disadvantages of the state of the art, in particular with regard to the severe side-effects, are at least partially eliminated.

The object according to the present invention is achieved by a process for the production of a pharmaceutical agent for oral or topical administration in the treatment of protozoal diseases, in particular of leishmaniasis, which contains as the active substance one or several compounds having the general formula I



(I)

in which R^1 is a saturated or monounsaturated or polyunsaturated hydrocarbon residue with 12 to 20 C atoms and R^2, R^3 and R^4 denote independently of one another hydrogen, a C_1-C_5 alkyl group, a C_3-C_6

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cycloalkyl group or a C_1-C_5 hydroxyalkyl group whereby two of the residues R^2, R^3 and R^4 can together form a C_2-C_5 alkylene group which, if desired, can be substituted with an -O-, -S- or NR^5 group, in which R^5 is hydrogen, a C_1-C_5 alkyl group, a C_3-C_6 cycloalkyl group or a C_1-C_5 hydroxyalkyl group as well as, if desired the usual pharmaceutical auxiliary, diluting, carrier or/and filling substances.

In the general formula I, R^1 can be branched or straight-chained. R^1 is preferably a straight-chained hydrocarbon residue with 16 to 20 C atoms, in particular a hexadecyl, octadecyl, oleyl, elaidyl, eicosyl or eicosenyl-cis-(ω-9) residue. R^1 is particularly preferably a hexadecyl or octadecyl residue.

Examples of suitable residues R^2, R^3 and R^4 in the formula I are for instance methyl, ethyl, propyl, butyl and pentyl residues, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl residues, hydroxymethyl, hydroxyethyl and hydroxypropyl residues. Two of the residues R^2, R^3 and R^4 can for example form a pyrrolidine, a piperidine or a morpholine group. At least one of the residues R^2, R^3 and R^4 is preferably different from hydrogen, it is particularly preferred that all 3 residues are different from hydrogen.

Examples of preferred residues R^2, R^3 and R^4 are methyl, ethyl, hydroxyethyl and C_3-C_6 cycloalkyl residues. If one of R^2, R^3 and R^4 is a cycloalkyl residue, then the other two residues are preferably methyl residues. It is particularly preferred that the residues R^2, R^3 and R^4 are independently of each other methyl or ethyl residues. It is most preferred when R^2, R^3 and R^4 are methyl residues so that alkyl phosphocholines represent

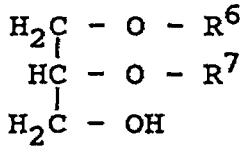
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a particularly preferred class of compounds which is suitable for the production of an agent against protozoal diseases, in particular against leishmaniasis.

It was surprisingly found that compounds having the general formula I when administered orally or topically show no measurable side-effects and a very much higher activity than sodium stibogluconate. In any case the therapeutic agents according to the present invention constitute the first forms of oral therapy for leishmaniasis diseases, and they are considerably more effective than Pentostam, a standard therapeutic preparation used worldwide in the liver and in particular also in the spleen.

In a preferred embodiment of the present invention the oral or topical therapeutic preparation additionally contains one or several alkyl glycerols having the general formula II



(II)

in which one of the residues R^6 and R^7 denotes an alkyl group with 2 to 12 C atoms and the other residue denotes a hydrogen atom. An alkyl glycerol mixture is preferably used which contains nonyl or octyl glycerol, hexyl or pentyl glycerol and propyl or ethyl glycerol as well as, if desired, water.

The pharmaceutical agent according to the present invention contains in one dosage unit preferably 5 to 2000 mg, particularly preferably 10 to 500 mg of one or

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several compounds having the general formula I. For topical administration the pharmaceutical agent according to the present invention preferably contains 5 to 200 mg of one or several compounds having the general formula I per ml of an alkyl glycerol having the formula II or of a corresponding alkyl glycerol mixture.

For oral administration the pharmaceutical agent according to the present invention is preferably formulated as a drinking solution with a daily dosage between 1 and 10 mg/kg of one or several compounds having the general formula I.

The production of an oral pharmaceutical agent according to the present invention can on the other hand also be carried out by mixing or homogenizing one or several compounds having the general formula I with the usual physiologically tolerated filling, carrier, dilution or/and auxiliary substances at temperatures between 20 and 120°C and, if desired in order to prepare formulations which contain 10 to 800 mg of compounds having the general formula I in one dosage unit, the mixture thus obtained is poured into hollow cells of an appropriate size or filled into capsules of an appropriate size or granulated and then pressed into tablets, if desired, with addition of further common auxiliary substances. The active substance can for example be mixed with one or several of the following auxiliary substances: starch, cellulose, lactose, formalin-casein, modified starch, magnesium stearate, calcium hydrogenphosphate, highly-dispersed silicic acid, talcum and phenoxyethanol. The mixture obtained is granulated, if desired, with an aqueous solution containing for example gelatin, starch, polyvinyl pyrrolidone, vinylpyrrolidon-vinyl acetate

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copolymerisate or/and polyoxyethylene sobitanmonooleate, as constituent and the granulate is homogenized, if desired, with one or several of the aforementioned auxiliary substances. Subsequently this mixture can be pressed into tablets or filled into capsules whereby the tablets or capsules each contain 10 to 800 mg of active substance in one dosage unit.

In a particularly preferred embodiment the active substance is suspended with soybean lecithin as well as, if desired, 0.1 to 0.5 parts by weight phenoxyethanol (in relation to one part by weight of the active substance) at temperatures between 33 and 37°C in melted resin fat and homogenized and subsequently the mixture is poured into hollow cells whereby one dosage unit contains 10 to 800 mg of the active substance.

Moreover the active substance can be homogenized at a temperature between 50 and 120°C, if desired in the presence of one or several emulsifiers or/and 0.1 - 0.5 parts by weight phenoxyethanol (in relation to 1 part by weight of the active substance) with at least one of the following substances: paraffin, vaseline, aliphatic alcohol with 12 to 25 C atoms, sorbitanmonopalmitate, aliphatic monocarboxylic acid with 15 to 20 C atoms, polyoxyethylenepolyol fatty acid ester. If desired, the mixture obtained can be emulsified with addition of a multivalent lower (preferably C_2-C_3) aliphatic alcohol (e.g. ethylene glycol, diethylene glycol, propylene glycol, dipropylene glycol and in particular glycerol).

On the other hand, if desired, the active substance can be dissolved at temperatures between 30 and 100°C in the presence of 0.1 - 0.5 parts by weight phenoxyethanol (in relation to one part by weight of the active substance)

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as well as, if desired, in the presence of an emulsifier and if desired the solution thus obtained is filled up with sufficient water or vegetable oil so that the final solution contains 0.1 to 5 % by weight of the active substance.

The active substance can also be mixed together with an alkyl glycerol having the general formula II or with a mixture of such alkyl glycerols as well as, if desired, water in which 1 to 30 parts by weight alkyl glycerol having the general formula II or of a corresponding alkyl mixture and if desired 1 to 30 parts by weight water, each in relation to 1 part by weight active substance according to general formula I, are used.

The present invention also concerns the use of one or several compounds having the general formula I as the active substance for an oral or a topical agent for treating protozoal diseases, in particular leishmaniasis. In this connection the agent can additionally contain one or several alkyl glycerols having the general formula II, in particular for topical applications.

Finally the invention also concerns a process for the treatment of protozoal diseases, in particular of leishmaniasis, which is characterized in that a pharmaceutical agent produced according to the present invention is administered topically or orally.

The production of compounds having the general formula I is described in detail in the examples for hexadecyl-phosphocholine. Further methods for the production of compounds having the general formula I are described for

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example in DE-A 27 52 125, DE-A 36 41 379, DE-A 36 41 491, DE-A 40 13 632, DE-A 36 41 377, the literature cited in these or in earlier patent applications or patent specifications of the same applicant. Reference is expressly made to this literature for the present patent application.

The pharmaceutical agents according to the present invention are preferably used for the treatment of leishmaniasis. Other protozoal diseases which can be treated by the agent according to the present invention are for instance malaria, trypanosomiasis, toxoplasmosis, babesiosis, amoebic dysentery and lambliasis. The agents according to the present invention are in particular suitable for those diseases in which the pathogen is present in organs such as the liver, spleen or kidney.

It is intended to elucidate the invention further by the following examples.

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Example 1

Production of hexadecylphosphocholine·H_2O

a) Hexadecylphosphoethanolamine
(phosphorylation, ring closure and ring opening)

Hexadecanol (1 mole, 243 g) and triethylamine (1.8 mole, 180 g) are dissolved in 1.5 l THF (tetrahydrofuran) and added dropwise to a solution of phosphoroxychloride (1.2 mole, 184 g) in 120 ml THF which was stirred vigorously in such a way that the temperature in the reaction vessel (three-neck, 5 l, with dropping funnel, thermometer and stirrer) does not exceed 10°C. In order to accelerate the process, the reaction vessel is cooled with an ice-salt mixture. The reaction is completed immediatly after the dropwise addition (detected by TLC in ether: Rf values of 0.8 for the initial product, of 0.0 for the reaction product after hydrolysis with water).

The ice-bath is removed and a solution of ethanolamine (1.5 mole, 92 g) and triethylamine (1.8 mole, 180 g) in 1 l dioxan are added while stirring vigorously in such a way that the temperature in the reaction vessel increases to 65 to 70°C. Then the ring formation is completed (detected by TLC in ether: Rf values of 0.2). Precipitated triethylamine hydrochloride is removed by filtration while still warm and 1.5 l 2N formic acid is added to the filtrate at 40 to 50°C. After 15 minutes the ring opening is completed (detected by TLC in ether: Rf values 0.0; TLC in chloroform/methanol/acetic acid/water 100:60:20:5 by volume: Rf value 0.8). It is cooled to -20°C and the precipitate which is mainly composed of pure hexadecylphosphoethanolamine is filtered off. If slight impurities are present a subsequent chromatographic purification is carried out.

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Microanalysis (MW 365.50):

calc. (%)	C 59.15	H 11.03	N 3.83	P 8.48
found (%)	59.01	10.95	3.79	8.31

Methylation of hexadecylphosphoethanolamine

The crystals obtained according to example 1 are taken up in 1.2 l 2-propanol and 0.4 l dichloromethane without further purification. Potassium carbonate (4 mole, 560 g) is added to the suspension of the crystals in 1 l water while stirring vigorously. Dimethyl sulfate (4 mole, 500 g) is added dropwise to the two-phase reaction mixture while stirring in such a way that the temperature does not exceed 40°C. The reaction is completed 60 minutes after the dropwise addition (detected by TLC in chloroform/methanol/25 % ammonia 50:50:5 by volume: Rf value 0.3). After phase separation at 20°C, the upper phase contains the product. The solvent is removed in a rotary evaporator under a vacuum and the viscous residue is chromatographed on silica gel (Merck product No. 7733, silica gel 60, particle size 0.2 to 0.5 mm).

Chromatography

Chloroform/methanol/25 % ammonia (200/15/1 by volume) is added to 2 kg silica gel and filled into a chromatography column. The viscous oil is dissolved in 800 ml of the above solvent mixture and the crude product is applied to the column (insoluble components are previously removed by filtration). It is eluted with mobile solvents of increasing polarity until the impurities are washed out. The product is finally eluted with chloroform/methanol/25 % ammonia (50/50/5 by

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volume). The combined eluates are rotary evaporated and the remaining water is removed with toluol. The residue is taken up in 600 ml dichloromethane and 4 l acetone is added. The crystals which separate out at -20°C are washed with cold acetone, then with pentane and dried in a vacuum. The yield of pure hexadecylphospocholine is 250 g (ca. 70 % in relation to hexadecylglycerol).
Microanalysis (MW 407.58):

calc. (%):	C 59.27	H 11.37	N 3.29	P 7.28
found (%):	58.98	11.31	3.21	7.11

Production of pharmaceutical formulations

Example for a solution:
25 g 1-n-propyloxy-2,3-propanediol, 12.5 g 1-n-hexyloxy-2,3-propanediol, 12.5 g 1-n-nonyloxy-2,3-propanediol, 44 g water and 1 g phenoxyethanol are mixed and 5 g hexadecylphosphocholine is dissolved in this mixture. The solution is freed of visible particles by filtration over suitable filters.
1 g solution contains 50 mg hexadecylphosphocholine.

Example for a an ointment:
5 g hexadecylphosphocholine is suspended in 35 g viscous paraffin, 30 g emulsified cetylstearyl alcohol and 30 g white vaseline are added and melted. This melt is first stirred until it has cooled down. A homogeneous distribution of active substance is achieved by processing the cooled melt by means of a suitable homogenizer (e.g. three-roll mill).
1 g of the hydrophilic ointment contains 50 mg hexadecylphosphocholine.

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Example for an emulsion:
11.83 g 1-n-propyloxy-2,3-propanediol, 5.91 g 1-n-hexaloxy-2,3-propanediol, 5.91 g 1-n-nonyloxy-2,3-propanediol, 20.35 g water and 1.0 g phenoxyethanol are mixed and 5 g hexadecylphosphocholine is dissolved in this mixture. 30 g white vaseline, 15 g cetylalcohol and 5 g sorbitan monopalmitate are melted on a water-bath, heated to 70°C and the solution of the active substance, which was also heated to 70°C, is emulsified in the fat phase with the aid of a high-speed dispersing apparatus. The cream is subsequently cooled down to 30°C while stirring. 1 g water-in-oil cream contains 50 mg hexadecylphosphocholine.

Example for capsules:
1.25 kg hexadecylphospocholine is dissolved in 5 kg chloroform and 1.25 kg aerosil is suspended in this solution. The solvent is subsequently removed in a vacuum. The dry mass is passed through a 1 mm sieve and dried once again in a vacuum at 30°C in order to remove any last remains of solvent. This granulate is filled in a known way to 500 mg into gelatin hard capsules with a size of 00 using a suitable capsule machine.
One capsule contains 250 mg hexadecylphosphocholine.

Examples of further active substances

Example 2
Octadecylphosphocholine
$C_{23}H_{50}NO_4P$ MW 435.630

Example 3
Oleylphosphocholine
$C_{23}H_{48}NO_4P$ MW 433.614

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Example 4
Elaidylphosphocholine
$C_{23}H_{48}NO_4P$ MW 433.614

Example 5
Hexadecylphospho-(N.N-dimethyl-N-ethyl)ethanolamine MW 421.603

Example 6
Octadecylphospho-(N.N-dimethyl-N-ethyl)ethanolamine MW 449.657

Example 7
Oleylphospho-(N.N-dimethyl-N-ethyl)ethanolamine MW 447.641

Example 8
Elaidylphospho-(N.N-dimethyl-N-ethyl)ethanolamine MW 447.641

Example 9
Hexadecylphospho-(N-cyclopropyl-N.N-dimethyl)-ethanolamine
$C_{23}H_{48}NO_4P$ MW 443.614

Example 10
Hexadecylphospho-(N-cyclobutyl-N.N-dimethyl)-ethanolamine
$C_{24}H_{50}NO_4P$ MW 447.641

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Example 11
Hexadecylphospho-(N-cyclopentyl-N.N-dimethyl)-ethanolamine
$C_{25}H_{52}NO_4P$ MW 461.668

Example 12
Hexadecylphospho-(N.N-dimethyl-N-hydroxyethyl)-ethanolamine
$C_{22}H_{48}NO_5P$ MW 437.602

Example 13
Hexadecylphospho-(N-methyl)-pyrrolidino-ethyl ester
$C_{23}H_{48}NO_4P$ MW 433.614

Example 14
Octadecylphospho-(N.N-diethyl-N-methyl)-ethanolamine
$C_{25}H_{54}NO_4P$ MW 463.684

Example 15
Octadecylphospho-(N-cyclopropyl-N.N-dimethyl)-ethanolamine
$C_{25}H_{52}NO_4P$ MW 461.668

Example 16
Octadecylphospho-(N-cyclobutyl-N.N-dimethyl)-ethanolamine
$C_{26}H_{54}NO_4P$ MW 475.695

Example 17
Octadecylphospho-(N-cyclopentyl-N.N-dimethyl)-ethanolamine
$C_{27}H_{56}NO_4P$ MW 489.722

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Example 18
Octadecylphospho-(N.N-dimethyl-N-hydroxyethyl)-ethanolamine
$C_{24}H_{52}NO_4P$ MW 465.656

Example 19
Octadecylphospho-(N-methyl)-pyrrolidino-ethyl ester
$C_{25}H_{52}NO_4P$ MW 461.668

Example 20
Oleylphospho-(N.N-diethyl-N-methyl)-ethanolamine
$C_{25}H_{52}NO_4P$ MW 461.668

Example 21
Oleylphospho-(N-cyclopropyl-N.N-dimethyl)-ethanolamine
$C_{25}H_{50}NO_4P$ MW 459.652

Example 22
Oleylphospho-(N-cyclopentyl-N.N-dimethyl)-ethanolamine
$C_{27}H_{54}NO_4P$ MW 487.706

Example 23
Oleylphospho-(n.N-dimethyl-N-hydroxyethyl)-ethanolamine
$C_{24}H_{50}NO_5P$ MW 463.640

Example 24
Oleylphospho-(N-methyl)-pyrrolidino-ethyl ester
$C_{25}H_{50}NO_4P$ MW 459.652

Example 25
Elaidylphospho-(N-cyclopropyl-N.N-dimethyl)-ethanolamine
$C_{25}H_{50}NO_4P$ MW 459.652

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Example 26
Elaidylphospho-(N.N-dimethyl-N-hydroxyethyl)-ethanolamine
$C_{24}H_{50}NO_5P$ MW 463.640

Example 27
Elaidylphospho-(N-methyl)-pyrrolidino-ethyl ester
$C_{25}H_{50}NO_4P$ MW 459.652

Example 28
Eicosylphosphocholine
$C_{25}H_{54}NO_4P$ MW 463.684

Example 29
Eicosylphospho-(N-ethyl-N.N-dimethyl)-ethanolamine
$C_{26}H_{56}NO_4P$ MW 477.711

Example 30
Eicosylphospho-(N.N-diethyl-N-methyl)-ethanolamine
$C_{27}H_{54}NO_4P$ MW 491.738

Example 31
Eicosylphospho-(N-cyclopropyl-N.N-dimethyl)-ethanolamine
$C_{27}H_{56}NO_4P$ MW 489.722

Example 32
Eicosylphospho-(N.N-dimethyl-N-hydroxyethyl)-ethanolamine
$C_{26}H_{56}NO_5P$ MW 493.710

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Example 33
Eicosylphospho-(N.N-dihydroxyethyl-N-methyl)-ethanolamine
$C_{27}H_{58}NO_6P$ MW 523.736

Example 34
Eicosylphospho-(N-methyl)-pyrrolidino-ethyl ester
$C_{27}H_{56}NO_4P$ MW 489.722

Example 35
Eicosenyl-cis-(ω-9)-phosphocholine
$C_{25}H_{52}NO_4P$ MW 461.668

Example 36
Eicosenyl-cis-(ω-9)-phospho-(N-ethyl-N.N-dimethyl)-ethanolamine
$C_{26}H_{54}NO_4P$ MW 475.695

Example 37
Eicosenyl-cis-(ω-9)-phospho-(N-cyclopropyl-N.N-dimethyl)-ethanolamine
$C_{27}H_{54}NO_4P$ MW 487.706

Example 38
Eicosenyl-cis-(ω-9)-phospho-(N.N-dimethyl-N-hydroxyethyl)-ethanolamine
$C_{26}H_{54}NO_5P$ MW 491.694

Example 39
Effect of various leishmaniasis drugs on the presence of pathogens in the liver of experimental animals (rats) infected with L. donovani.

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The effect of the phospholipids according to the present invention (hexadecylphosphocholine, octadecylphosphocholine and oleylphospho-(N.N-dimethyl-N-ethyl)-ethanolamine) was compared with the standard therapeutic agent Pentostam used worldwide and the ether lipid $Et_{18}OCH_3$ (1-octadecyl-2-methyl-rac-glycero-3-phosphocholine).

The compounds according to the present invention and $Et_{18}OCH_3$ were administered orally while Pentostam was administered intravenously. It was found that the alkyl phosphocholines with a C_{18} and C_{16} chain were 32-times more effective than the standard therapeutic agent Pentostam while olely-phospho-(N.N-dimethyl-N-ethyl)ethanolamine has a comparable effect to Pentostam.

The results of this experiment are shown in Table 1. The number of pathogens per liver was determined by microscopic analysis.

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Table 1
Number of leishmania pathogens in the liver after a 3 week period of therapy

	Pathogens per liver (in millions)	Relative effectiveness (pathogens per liver after Pentostam therapy divided by pathogens/liver after addition of test substance)
Control	536.9	---
1-octadecyl-2-methyl-rac-glycero-3-phospho-choline[1]	424.7	0.007
Oleylphospho-(N.N-dimethyl-N-ethyl)-ethanolamine[1]	4.7	0.7
Pentostam[2]	3.2	1.0
Hexadecylphospho-choline[1]	0.1	32.0
Octadecylphospho-choline[1]	0.1	32.0

[1] Alkyl-PC and $Et_{18}OCH_3$ - orally: 5 x 20 mg/kg/week for 3 weeks
[2] Pentostam - iv.: 5 x 120 mg/kg/week for 3 weeks

In some additional experiments parasites were no longer microscopically detectable in the liver and in the spleen after single oral dose of 200 mg hexadecylphosphocholine.

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Example 40
Effect of different leishmaniasis drugs on the presence of pathogens in the spleen

The experimental procedure was as described in example 39. The results of these experiments are shown in Table II.

Table II
Number of leishmania pathogens in the spleen after a 3 week period of therapy

	Pathogens per spleen (in millions)	Relative effectiveness (pathogens per spleen after Pentostam therapy divided by pathogens/spleen after addition of test substance)
Control	24.3	---
1-octadecyl-2-methyl-rac-glycero-3-phospho-choline	6.5	0.9
Oleylphospho-(N.N-dimethyl-N-ethyl)-ethanolamine[1]	0.03	210.0
Pentostam	6.3	1.0
Hexadecylphospho-choline	0.01	630.0
Octadecylphospho-choline	0.01	630.0

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The weak effect of Pentostam in the spleen is surprising. The alkylphosphocholines are in this case > 600-fold more effective than the standard therapy.

In several additional experiments parasites were no longer microscopically detectable after a single oral dose of 200 mg hexadecylphosphocholine.

Table III shows the concentration of hexadecylphosphocholine (C_{16}-O-PC), octadecylphosphocholine (C_{18}-O-PC) and 1-octadecyl-2-methyl-rac-glycero-3-phosphocholine ($Et_{18}OCH_3$) in the organs of the rat after oral administration of 50 µmol/day for 5 days, a pause of 2 days then for a further 4 days at 50 µmol/day.

Table III

Organ	Amount of substance (nmol/g fresh tissue)		
	C_{16}-O-PC	C_{18}-O-PC	$Et_{18}OCH_3$
Serum	130	47	5
Liver	272	298	36
Spleen	410	424	43
Kidney	853	406	57

It is surprising how well hexadecylphosphocholine and octadecylphosphocholine accumulate in the spleen. It is especially in the spleen that the standard therapeutic agent Pentostam has an extremely low effectiveness. In comparison to this $Et_{18}OCH_3$ is only present in the spleen and in the liver in extremely low concentrations.

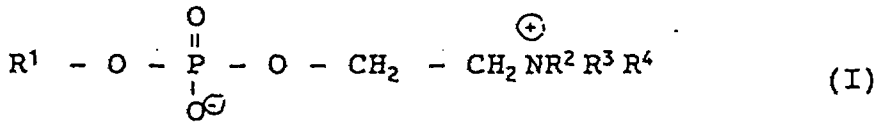
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C l a i m s

1. Process for the production of a pharmaceutical agent for oral or topical administration in the treatment of protozoal diseases, in particular of leishmaniasis, which contains as the active substance one or several compounds having the general formula I



(I)

in which R^1 is a saturated or monounsaturated or polyunsaturated hydrocarbon residue with 12 to 20 C atoms and R^2, R^3 and R^4 denote independently of one another hydrogen, a C_1-C_5 alkyl group, a C_3-C_6 cycloalkyl group or a C_1-C_5 hydroxyalkyl group whereby two of the residues R^2, R^3 and R^4 can together form a C_2-C_5 alkylene group which, if desired, can be substituted with an -O-, -S- or NR^5 group, in which R^5 is hydrogen, a C_1-C_5 alkyl group, a C_3-C_6 cycloalkyl group or a C_1-C_5 hydroxyalkyl group as well as, if desired the usual pharmaceutical auxiliary, diluting, carrier or/and filling substances.

2. Process as claimed in claim 1,
w h e r e i n
R^1 is straight-chained and has 16 to 20 C atoms.

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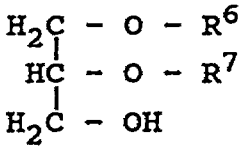
3. Process as claimed in claim 1,
w h e r e i n
the residues R^2, R^3 and R^4 are independently of each other methyl, ethyl, hydroxyethyl or C_3-C_6 cycloalkyl residues.

4. Process as claimed in claim 3,
w h e r e i n
R^2, R^3 and R^4 are methyl residues.

5. Process as claimed in one of the previous claims,
w h e r e i n
R^1 is a hexadecyl, octadecyl, oleyl, elaidyl, eicosyl or eicosenyl-cis(ω-9) residue.

6. Process as claimed in claim 5,
w h e r e i n
R^1 is a hexadecyl or octadecyl residue.

7. Process as claimed in one of the previous claims,
w h e r e i n
the pharmaceutical agent additionally contains one or several alkyl glycerols having the general formula II



(II)

in which one of the residues R^6 and R^7 denotes an alkyl group with 2 to 12 C atoms and the other residue denotes a hydrogen atom.

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8. Process as claimed in claim 7,
w h e r e i n
the pharmaceutical agent contains an alkyl glycerol mixture of nonyl or octyl glycerol, hexyl or pentyl glycerol and propyl or ethyl glycerol as well as, if desired, water.

9. Process as claimed in one of the previous claims,
w h e r e i n
the pharmaceutical agent contains 5 to 2000 mg, in particular 10 to 500 mg, of one or several compounds having the general formula I in one dosage unit.

10. Process as claimed in one of the previous claims,
w h e r e i n
it contains as a topical pharmaceutical agent 5 - 200 mg of one or several compounds having the general formula I per ml of an alkyl glycerol having the formula II or of a corresponding alkyl glycerol mixture.

11. Process as claimed in one of the claims 1 to 10,
w h e r e i n
it is formulated as a drinking solution having a daily dose between 1 and 10 mg/kg of one or several compounds having the general formula I.

12. Process as claimed in one of the claims 1 to 10,
w h e r e i n
one or several compounds having the general formula I are mixed or homogenized with the usual physiologically tolerated filling, carrier, dilution or/and auxiliary substances at

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temperatures between 20 and 120°C and, if desired, in order to prepare formulations which contain 10 to 800 mg of compounds having the general formula I in one dosage unit, the mixture thus obtained is poured into hollow cells of an appropriate size or filled into capsules of an appropriate size or granulated and then pressed into tablets, if desired, with addition of further common auxiliary substances.

13. Process as claimed in claim 12,
w h e r e i n
one or several compounds having the general formula I are mixed with one or several of the following auxiliary substances: starch, cellulose, lactose, formalin-casein, modified starch, magnesium stearate, calcium hydrogenphosphate, highly-dispersed silicic acid, talcum and phenoxyethanol, the mixture obtained is granulated if desired with an aqueous solution containing the constituents gelatin, starch, polyvinyl pyrrolidone, vinylpyrrolidone-vinyl acetate copolymerisate or/and polyoxyethylene sobitanmonooleate, the granulate is homogenized, if desired, with one or several of the aforementioned auxiliary substances and this mixture is pressed into tablets or filled into capsules whereby the tablets or capsules each contain 10 to 800 mg of compounds having the general formula I in one dosage unit.

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14. Process as claimed in one of the claims 12 or 13, w h e r e i n
one or several compounds having the general formula I are suspended with soybean lecithin as well as if desired, 0.1 to 0.5 parts by weight phenoxyethanol (in relation to one part by weight of compounds having the general formula I) at temperatures between 33 - 37°C in melted resin fat and homogenized and subsequently the mixture is poured into hollow cells whereby the dosage unit contains 10 to 800 mg of compounds having the formula I.

15. Process as claimed in one of the claims 12 or 13, w h e r e i n,
one or several compounds having the general formula I are homogenized at a temperature between 50 and 120°C, if desired, in the presence of one or several emulsifiers or/and 0.1 - 0.5 parts by weight phenoxyethanol (in relation to 1 part by weight of compounds having the formula I) with at least one of the following substances: paraffin, vaseline, aliphatic alcohols with 12 to 25 C atoms, sorbitanmonopalmitate, aliphatic monocarboxylic acid with 15 to 20 C atoms, polyoxyethylene polyol fatty acid ester, and the homogenized mixture is emulsified, if desired, with addition of a multivalent lower aliphatic alcohol.

16. Process as claimed in one of the claims 12 to 15, w h e r e i n
one or several compounds having the general formula I are dissolved at temperatures between 30 - 100°C, if desired, in the presence of 0.1 - 0.5 parts by weight phenoxyethanol (in relation to one part by weight of compounds having the formula I) as well

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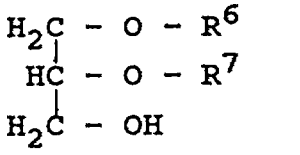
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as, if desired, in the presence of an emulsifier and if desired, the solution thus obtained is filled up with sufficient water or vegetable oil so that the final solution contains 0.1 - 5 percent by weight of compounds having the formula I.

17. Process as claimed in one of the claims 7 to 16, w h e r e i n
an alkyl glycerol is additionally used in the production having the formula II



(II)

in which one of the residues R^6 and R^7 denotes an alkyl group with 2 to 12 C atoms and the other residue denotes a hydrogen atom, or a mixture of such alkyl glycerols as well as, if desired, water is used whereby 1 - 30 parts by weight of an alkyl glycerol having the formula II or of a corresponding alkyl glycerol mixture and if desired 1 - 30 parts by weight of water, each in relation to 1 part by weight of compounds having the formula I, are used.

18. Use of one or several compounds having the general formula I defined in claim 1 for the treatment of protozoal diseases, in particular of leishmaniasis.

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19. Use as claimed in claim 18,
w h e r e i n
the agent additionally contains one or several alkyl glycerols having the general formula II defined in claim 7.

20. Process for the treatment of protozoal diseases, in particular of leishmaniasis,
w h e r e i n
a pharmaceutical agent as claimed in one of the claims 1 to 17 is administered topically or orally.

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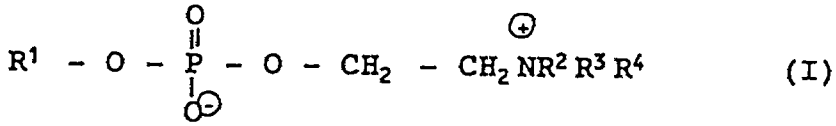
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PROCESS FOR THE PRODUCTION OF A PHARMACEUTICAL AGENT FOR ORAL OR TOPICAL ADMINISTRATION IN THE TREATMENT OF LEISHMANIASIS

A b s t r a c t

The invention concerns a new pharmaceutical agent for oral or topical administration in the treatment of protozoal diseases, in particular of leishmaniasis, which contains as the active substance one or several compounds having the general formula I



(I)

in which R^1 is a saturated or monounsaturated or polyunsaturated hydrocarbon residue with 12 to 20 C atoms and R^2, R^3 and R^4 denote independently of one another hydrogen, a C_1-C_5 alkyl group, a C_3-C_6 cycloalkyl group or a C_1-C_5 hydroxyalkyl group whereby two of the residues R^2, R^3 and R^4 can together form a C_2-C_5 alkylene group which, if desired, can be substituted with an -O-, -S- or NR^5 group, in which R^5 is hydrogen, a C_1-C_5 alkyl group, a C_3-C_6 cycloalkyl group or a C_1-C_5 hydroxyalkyl group as well as, if desired the usual pharmaceutical auxiliary, diluting, carrier or/and filling substances.

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Max-Planck-Gesellschaft
zur Förderung der Wissenschaften e.V.
Bunsenstraße 10
D - 3400 Göttingen

Process for the production of a pharmaceutical agent for oral or topical administration in the treatment of leishmaniasis

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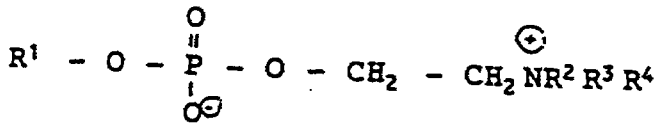
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☑ Claim(s) : paged 1/4 to paged 4/4.
☐ Drawing(s) : paged ..... to paged .....
☐ Abstract : paged ..... to paged .....

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New Claims

1. Use of compounds having the general formula I



(I)

in which R^1 is a saturated or monounsaturated or polyunsaturated hydrocarbon residue with 12 to 20 C-atoms and R^2, R^3 and R^4 independently of one another are hydrogen, a C_1-C_5 alkyl group, a C_3-C_6 cycloalkyl group or a C_1-C_5 hydroxyalkyl group, whereby two of the residues R^2, R^3 and R^4 can together form a C_2-C_5 alkylene group which, if desired, can be substituted with an -O-, -S- or NR^5 group, in which R^5 is hydrogen, a C_1-C_5 alkyl group, a C_3-C_6 cycloalkyl group or a C_1-C_5 hydroxyalkyl group as well as, if desired, additionally mixtures thereof containing usual pharmaceutical auxiliary, diluting, carrier or/and filling substances for the preparation of a pharmaceutical agent for the oral or topical treatment of leishmaniasis.

2. Use as claimed in claim 1,
wherein R^1 is straight-chained and has 16 to 20 C-atoms.



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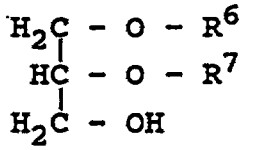
3. Use as claimed in claim 1,
w h e r e i n
the residues R^2, R^3 and R^4 are independently of each other methyl, ethyl, hydroxyethyl or C_3-C_6 cycloalkyl residues.

4. Use as claimed in claim 3,
w h e r e i n
R^2, R^3 and R^4 are methyl residues.

5. Use as claimed in one of the previous claims,
w h e r e i n
R^1 is a hexadecyl, octadecyl, oleyl, elaidyl, eicosyl or eicosenyl-cis(ω-9) residue.

6. Use as claimed in claim 5,
w h e r e i n
R^1 is a hexadecyl or octadecyl residue.

7. Use as claimed in one of the previous claims,
w h e r e i n
the pharmaceutical agent additionally contains one or several alkyl glycerols having the general formula II



(II)

in which one of the residues R^6 and R^7 denotes an alkyl group with 2 to 12 C atoms and the other residue denotes a hydrogen atom.

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8. Use as claimed in claim 7,
w h e r e i n
the pharmaceutical agent contains an alkyl glycerol mixture of nonyl or octyl glycerol, hexyl or pentyl glycerol and propyl or ethyl glycerol as well as, if desired, water.

9. Use as claimed in one of the previous claims,
w h e r e i n
the pharmaceutical agent contains 5 to 2000 mg, in particular 10 to 500 mg, of one or several compounds having the general formula I in one dosage unit.

10. Use as claimed in one of the previous claims,
w h e r e i n
it contains as a topical pharmaceutical agent 5 - 200 mg of one or several compounds having the general formula I per ml of an alkyl glycerol having the formula II or of a corresponding alkyl glycerol mixture.

11. Use as claimed in one of claims 1 to 10,
w h e r e i n
it is formulated as a drinking solution having a daily dose between 1 and 10 mg/kg of one or several compounds having the general formula I.

12. Use as claimed in one of claims 1 to 10,
w h e r e i n
one or several compounds having the general formula I are mixed or homogenized with the usual physiologically tolerated filling, carrier, dilution or/and auxiliary substances at

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temperatures between 20 and 120°C and, if desired, in order to prepare formulations which contain 10 to 800 mg of compounds having the general formula I in one dosage unit, the mixture thus obtained is poured into hollow cells of an appropriate size or filled into capsules of an appropriate size or granulated and then pressed into tablets, if desired, with addition of further common auxiliary substances.

13. Use as claimed in claim 12,

w h e r e i n

one or several compounds having the general formula I are mixed with one or several of the following auxiliary substances: starch, cellulose, lactose, formalin-casein, modified starch, magnesium stearate, calcium hydrogenphosphate, highly-dispersed silicic acid, talcum and phenoxyethanol, the mixture obtained is granulated if desired with an aqueous solution containing the constituents gelatin, starch, polyvinyl pyrrolidone, vinylpyrrolidone-vinyl acetate copolymerisate or/and polyoxyethylene sorbitanmonooleate, the granulate is homogenized, if desired, with one or several of the aforementioned auxiliary substances and this mixture is pressed into tablets or filled into capsules whereby the tablets or capsules each contain 10 to 800 mg of compounds having the general formula I in one dosage unit.

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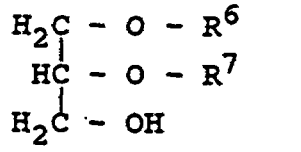
14. Use as claimed in one of claims 12 or 13,
w h e r e i n
one or several compounds having the general formula I are suspended with soybean lecithin as well as if desired, 0.1 to 0.5 parts by weight phenoxyethanol (in relation to one part by weight of compounds having the general formula I) at temperatures between 33 - 37°C in melted resin fat and homogenized and subsequently the mixture is poured into hollow cells whereby the dosage unit contains 10 to 800 mg of compounds having the formula I.

15. Use as claimed in one of claims 12 or 13,
w h e r e i n,
one or several compounds having the general formula I are homogenized at a temperature between 50 and 120°C, if desired, in the presence of one or several emulsifiers or/and 0.1 - 0.5 parts by weight phenoxyethanol (in relation to 1 part by weight of compounds having the formula I) with at least one of the following substances: paraffin, vaseline, aliphatic alcohols with 12 to 25 C atoms, sorbitanmonopalmitate, aliphatic monocarboxylic acid with 15 to 20 C atoms, polyoxyethylene polyol fatty acid ester, and the homogenized mixture is emulsified, if desired, with addition of a multivalent lower aliphatic alcohol.

16. Use as claimed in one of claims 12 to 15,
w h e r e i n
one or several compounds having the general formula I are dissolved at temperatures between 30 - 100°C, if desired, in the presence of 0.1 - 0.5 parts by weight phenoxyethanol (in relation to one part by weight of compounds having the formula I) as well

as, if desired, in the presence of an emulsifier and if desired, the solution thus obtained is filled up with sufficient water or vegetable oil so that the final solution contains 0.1 - 5 percent by weight of compounds having the formula I.

17. Use as claimed in one of claims 7 to 16,
w h e r e i n
an alkyl glycerol is additionally used in the production, having the formula II



(II)

in which one of the residues R^6 and R^7 denotes an alkyl group with 2 to 12 C atoms and the other residue denotes a hydrogen atom, or a mixture of such alkyl glycerols as well as, if desired, water is used whereby 1 - 30 parts by weight of an alkyl glycerol having the formula II or of a corresponding alkyl glycerol mixture and if desired 1 - 30 parts by weight of water, each in relation to 1 part by weight of compounds having the formula I, are used.

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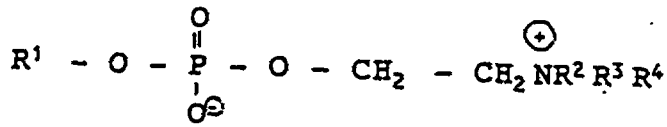
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particular C_{22} alkyl phosphocholines are active against Leishmania. It was, however, also established that the alkyl phosphocholines, in particular hexadecyl-phosphocholine, were highly toxic for the experimental animals, in particular for macrophages in therapeutically effective doses so that they do not represent a real alternative when administered subcutaneously to the known therapy with sodium stibogluconate.

Thus the object of the present invention was to provide a pharmaceutical agent for protozoal diseases, in particular for leishmaniasis, in which the disadvantages of the state of the art, in particular with regard to the severe side-effects, are at least partially eliminated.

The object of the invention is achieved by using one or several compounds having general formula I



(I)

in which R^1 is a saturated or monounsaturated or polyunsaturated hydrocarbon residue with 12 to 20 C atoms and R^2, R^3 and R^4 denote independently of one another hydrogen, a C_1-C_5 alkyl group, a C_3-C_6

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cycloalkyl group or a C_1-C_5 hydroxyalkyl group whereby two of the residues R^2, R^3 and R^4 can together form a C_2-C_5 alkylene group which, if desired, can be substituted with an -O-, -S- or NR^5 group, in which R^5 is hydrogen, a C_1-C_5 alkyl group, a C_3-C_6 cycloalkyl group or a C_1-C_5 hydroxyalkyl group as well as, if desired the usual pharmaceutical auxiliary, diluting, carrier or/and filling substances for the preparation of a pharmaceutical agent to be administered orally or topically in the treatment of leishmaniasis.

In the general formula I, R^1 can be branched or straight-chained. R^1 is preferably a straight-chained hydrocarbon residue with 16 to 20 C atoms, in particular a hexadecyl, octadecyl, oleyl, elaidyl, eicosyl or eicosenyl-cis-(ω-9) residue. R^1 is particularly preferably a hexadecyl or octadecyl residue.

Examples of suitable residues R^2, R^3 and R^4 in the formula I are for instance methyl, ethyl, propyl, butyl and pentyl residues, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl residues, hydroxymethyl, hydroxyethyl and hydroxypropyl residues. Two of the residues R^2, R^3 and R^4 can for example form a pyrrolidine, a piperidine or a morpholine group. At least one of the residues R^2, R^3 and R^4 is preferably different from hydrogen, it is particularly preferred that all 3 residues are different from hydrogen.

Examples of preferred residues R^2, R^3 and R^4 are methyl, ethyl, hydroxyethyl and C_3-C_6 cycloalkyl residues. If one of R^2, R^3 and R^4 is a cycloalkyl residue, then the other two residues are preferably methyl residues. It is particularly preferred that the residues R^2, R^3 and R^4 are independently of each other methyl or ethyl residues. It is most preferred when R^2, R^3 and R^4 are methyl residues so that alkyl phosphocholines represent

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several compounds having the general formula I. For topical administration the pharmaceutical agent according to the present invention preferably contains 5 to 200 mg of one or several compounds having the general formula I per ml of an alkyl glycerol having the formula II or of a corresponding alkyl glycerol mixture.

For oral administration the pharmaceutical agent according to the present invention is preferably formulated as a drinking solution with a daily dosage between 1 and 10 mg/kg of one or several compounds having the general formula I.

According to the invention the production of an oral pharmaceutical agent can, on the other hand, also be carried out by mixing or homogenizing one or several compounds having the general formula I with the usual physiologically tolerated filling, carrier, dilution or/and auxiliary substances at temperatures between 20 and 120°C and, if desired in order to prepare formulations which contain 10 to 800 mg of compounds having the general formula I in one dosage unit, the mixture thus obtained is poured into hollow cells of an appropriate size or filled into capsules of an appropriate size or granulated and then pressed into tablets, if desired, with addition of further common auxiliary substances. The active substance can for example be mixed with one or several of the following auxiliary substances: starch, cellulose, lactose, formalin-casein, modified starch, magnesium stearate, calcium hydrogenphosphate, highly-dispersed silicic acid, talcum and phenoxyethanol. The mixture obtained is granulated, if desired, with an aqueous solution containing for example gelatin, starch, polyvinyl pyrrolidone, vinylpyrrolidon-vinyl acetate

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as well as, if desired, in the presence of an emulsifier and if desired the solution thus obtained is filled up with sufficient water or vegetable oil so that the final solution contains 0.1 to 5 % by weight of the active substance.

The active substance can also be mixed together with an alkyl glycerol having the general formula II or with a mixture of such alkyl glycerols as well as, if desired, water in which 1 to 30 parts by weight alkyl glycerol having the general formula II or of a corresponding alkyl mixture and if desired 1 to 30 parts by weight water, each in relation to 1 part by weight active substance according to general formula I, are used.

The production of compounds having the general formula I is described in detail in the examples for hexadecyl-phosphocholine. Further methods for the production of compounds having the general formula I are described for

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example in DE-A 27 52 125, DE-A 36 41 379, DE-A 36 41 491, DE-A 40 13 632, DE-A 36 41 377, the literature cited in these or in earlier patent applications or patent specifications of the same applicant. Reference is expressly made to this literature for the present patent application.

It is intended to elucidate the invention further by the following examples.

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