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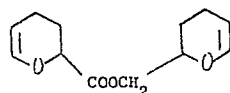
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⑤④ A pharmaceutical composition for tropical diseases.

⑤⑦ A pharmaceutical composition of prolonged effect in the treating of Tropical Diseases comprises an organic nitrogen base drug which is effective against diseases such as malaria, dispersed in a polymeric matrix of a copolymer of the compound



and a comonomer which contains more than one functional group selected from hydroxy and carboxy groups.

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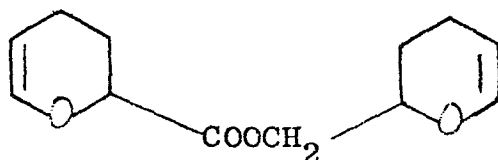
A Pharmaceutical Composition for Tropical Diseases

The present invention relates to pharmaceutical compositions for the treatment of tropical disease.

Tropical diseases, for example malaria and leprosy, have hitherto been prevented and treated by periodic administration of a dose of a drug to combat offending parasites present in the body. The drug is generally administered orally or by injection, and passes through the body so that frequent dosage is necessary.

An object of this invention is to provide a composition which is effective against tropical disease and which can provide a prolonged supply of a drug to a body with infrequent administration.

According to the present invention there is provided a composition for use in the treatment of tropical disease, comprising a drug which is an organic nitrogen compound of basic reaction and which is effective against tropical disease in admixture with a polymeric matrix of a copolymer of the compound of the formula



(I)

with at least one compound having more than one functional

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group selected from OH and COOH groups.

Drugs of particular effectiveness are, cycloguanil, pyrimethamine and sulphadiazine.

Drugs which are effective against tropical disease  
5 normally contain nitrogen atoms and are consequently basic in character. This can cause considerable problems in the preparation of the composition of this invention as the copolymerisation reaction between the compound of formula I and the compound or compounds having more than one OH or  
10 COOH group is acid catalysed; thus, admixture of such a drug with the copolymerisation reactants can result in a neutralisation reaction between the drug and the acid catalyst with consequent prevention or restriction of the copolymerisation.

15 Strongly basic drugs, if soluble in the copolymerisation reaction medium, therefore inhibit the copolymer formation, and this can be overcome either (a) by selecting an insoluble drug or rendering the drug insoluble and forming a dispersion rather than a solution, or (b) by using the  
20 drug in the form of its salt, preferably fully neutralised.

The use of soluble bases requires very large amounts of acid catalyst for the copolymerisation.

Examples of tropical disease which can be prevented or treated by compositions of this invention are malaria,  
25 leprosy, schistosomiasis and clonorchiasis.

Examples of drugs which can be used in the present composition to combat these and other tropical diseases are quinine, sulphonamides, chlorphenyl derivatives, chloroguanide, pyrimethamine, trimethoprim, quinoline derivatives such as  
30 pamaquine, chloroquine, pentaquine, primaquine and

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amodiaquine, pararosaniline, sulphamethizole, dapsone,  
sodium sulphoxone, sulphetrone, sodium hydnochrome  
and sodium chaulmoograte.

The compound having two or more groups selected from  
5 OH and COOH groups is preferably a compound which occurs  
naturally in and/or is benign to the human body. Examples  
of compounds containing two or more groups selected from  
OH and COOH groups which can be used in the present  
invention are:

10 (a) among the compounds having two or more OH groups,  
glycerol, sorbitol, erythritol, inositol, glycols based on  
polyethylene oxide, 4,4' - dihydroxyphenyl - 2,2-propane,  
1,2-dihydroxy-benzene, 1,3-dihydroxy-benzene, 1,4-dihydroxy-  
benzene, 1,2,3-trihydroxy-benzene, 1,2,4-trihydroxy-benzene,  
15 1,3,5-trihydroxy-benzene and the like;

(b) among the compounds having at least one OH group  
and at least one COOH group, lactic acid, malic acid, 2-  
hydroxyisobutyric acid, 10-hydroxydecanoic acid, 12-hydroxy-  
octadecanoic acid, 12-hydroxy- (cis) -9-octadecenoic acid,  
20 2-hydroxycyclo-hexanecarboxylic acid (hexahydrosalicylic acid),  
2-hydroxy-2-phenyl-(D)- propionic acid, diphenylhydroxyacetic  
acid, ascorbic acid, citric acid, tartaric acid, 2 hydroxy-3-  
methyl-(D) succinic acid, 2-hydroxybenzoic acid, 3-hydro-  
xybenzoic acid, 4-hydroxybenzoic acid, 2,3-dihydroxybenzoic  
25 acid, 2,4-dihydroxybenzoic acid, 2,5-dihydroxybenzoic acid,  
2,6-dihydroxybenzoic acid, 2,3,4-trihydroxybenzoic acid, 2,4,  
5-trihydroxybenzoic acid, 2,4,6-trihydroxybenzoic acid, 3,  
4,5-trihydroxybenzoic acid and the like;

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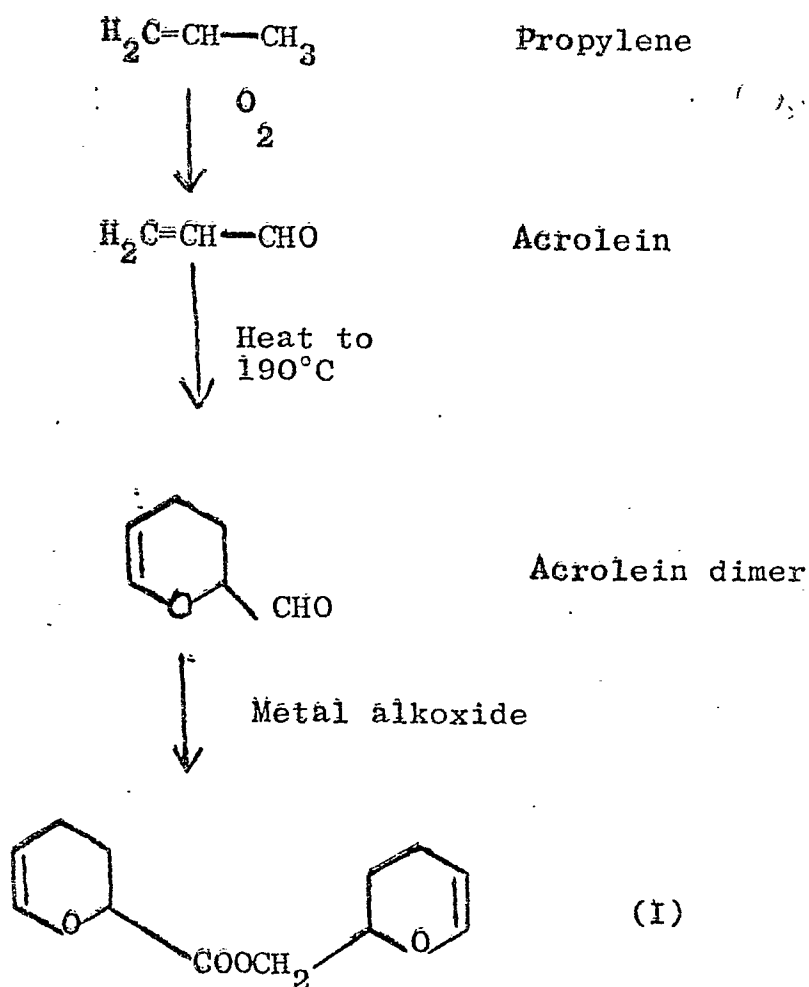
(c) among the compounds having two or more COOH groups, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, 1,2-cyclohexanedicarboxylic acid, 1,3-cyclohexanedicarboxylic acid, 1,4-cyclohexanedicarboxylic acid, phthalic acid, isophthalic acid, teraphthalic acid and the like.

The ratio of drug to copolymer which can be present in the compositions of this invention can vary within wide limits. Preferably the weight of the drug is at least about equal to the weight of copolymer, and it may be possible to have a steroid to copolymer weight ratio of up to 90:10. A steroid to copolymer ratio of from about 50:50 by weight to about 60:40 by weight is particularly suitable.

According to the process provided by the present invention, the compositions of this invention are prepared by copolymerising a compound of formula I hereinbefore with at least one compound having more than one group selected from OH and COOH groups in the presence of an acidic catalyst and in the presence of a drug effective against tropical disease.

The compound of formula I hereinbefore, which is a mixture of stereoisomers, is a colourless liquid having a high boiling point, a very low level of oral toxicity and no known detrimental effect on skin. It may be prepared according to the following reaction sequence:

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The process provided by the present invention may be carried out by simply mixing the compound of formula I with a compound having two or more groups selected from OH and COOH groups or with a mixture of such compounds in the presence of an acidic catalyst, advantageously at an elevated temperature such as from about  $60^\circ\text{C}$  to  $100^\circ\text{C}$ , especially at about  $80^\circ\text{C}$ , and then adding to the resulting mixture and homogeneously distributing therein the appropriate amount of the desired drug. The mixture thus obtained can then be allowed to cure, suitably at an elevated temperature.

It is preferable that the drug should not react with the

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catalyst, and it may therefore be in the form of a salt, for example its hydrochloride, or be insoluble in the reaction medium.

In certain circumstances it may be desirable to interrupt the copolymerisation during the initial mixing of the compound of formula I with a compound having two or more groups selected from OH and COOH groups or with a mixture of such compounds. This can be effected, for example, by the addition of an amount of a primary, secondary or tertiary amine such as triethylamine, a quaternary ammonium hydroxide or a basic inorganic oxide or hydroxide sufficient to neutralise the activity of the acidic catalyst. The drug preferably in salt form or in dispersion, can then be added to and homogeneously distributed in the resulting mixture and subsequently the copolymerisation can be allowed to proceed to completion by the addition of further acidic catalyst.

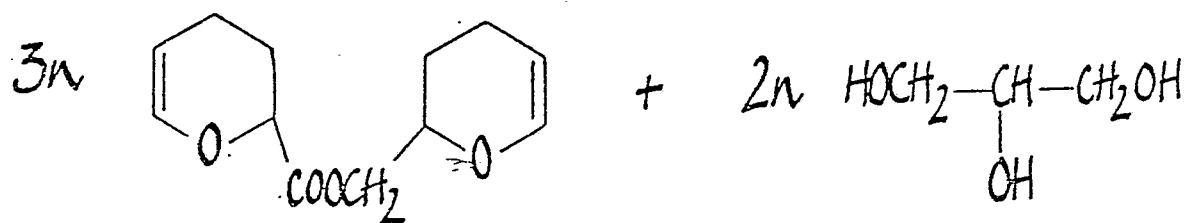
Suitable acidic catalysts which may be used in the present process include inorganic acids such as hydrochloric acid, sulphuric acid etc, organic acids such as paratoluenesulphonic acid etc and Lewis acids such as zinc chloride, tin tetrachloride, aluminium chloride, ferric chloride etc. The preferred acidic catalyst is ferric chloride. The amount of acidic catalyst used is not critical, but it is expedient to use from about 0.01% to 2.0%, particularly from about 0.04% to about 1.0% based on the total weight of the mixture.

The ratio of the compound of formula I to the compound having

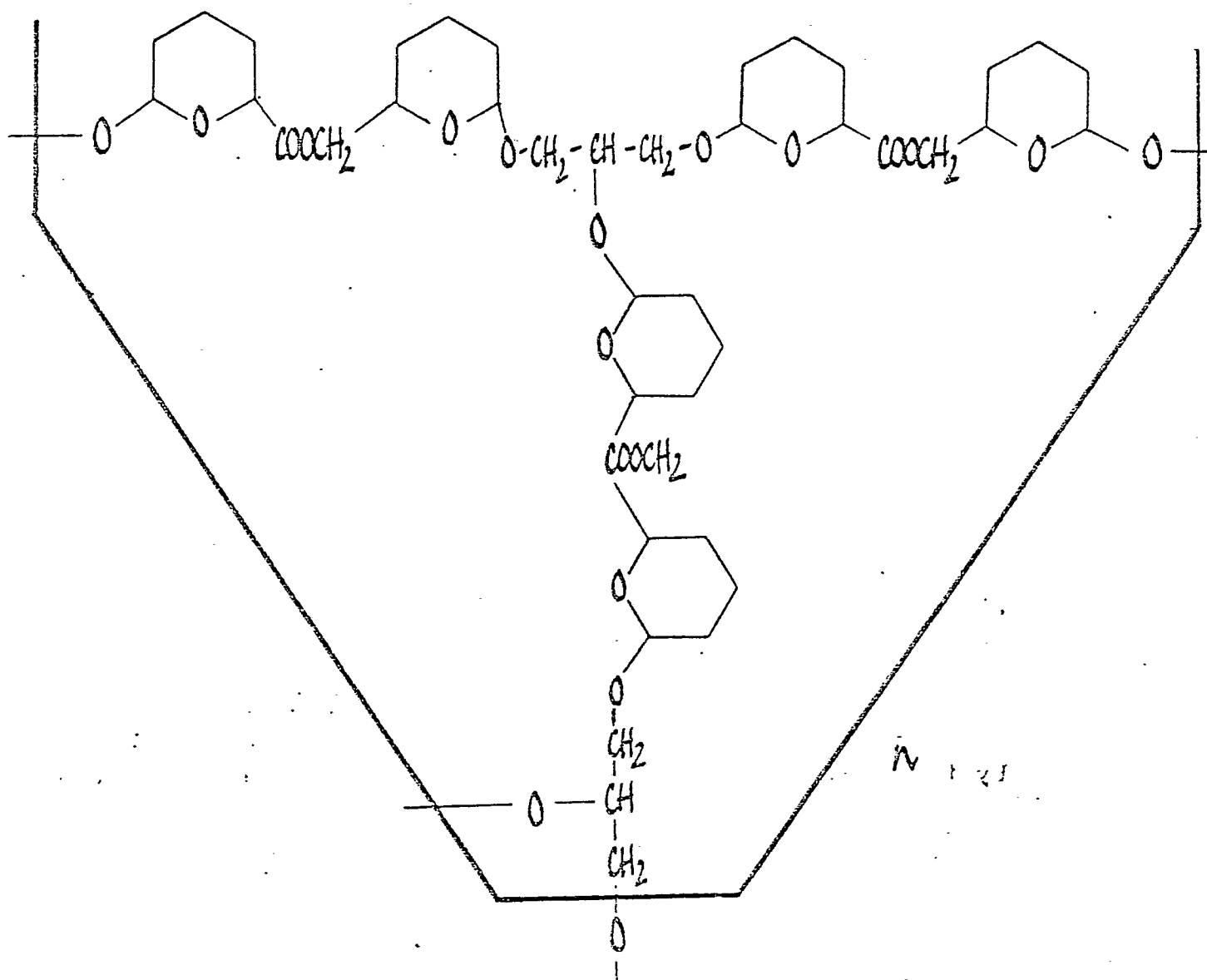


two or more groups selected from OH and COOH groups varied. It is convenient to use stoichiometric amounts, although the use of amounts which deviate considerably from stoichiometry is also possible.

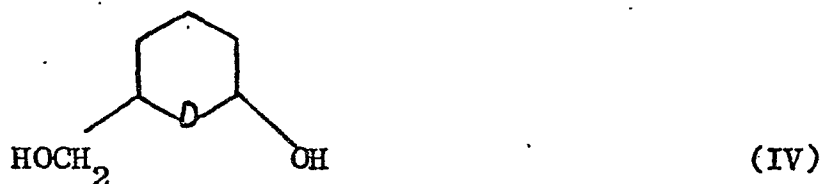
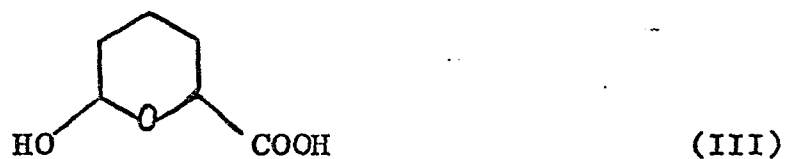
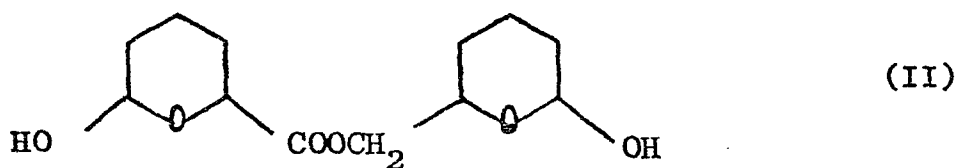
- 5 The copolymerisation may also be carried out in the presence of an inert pharmaceutically acceptable solvent or an inert pharmaceutically acceptable oil, whereby the nature of the resulting medicinal composition is modified. An example of such an oil is olive oil. The inert pharmaceut-
- 10 ically acceptable solvent or oil may be added as such or it may serve as a solvent or dispersant for other components of the copolymerisation mixture. Thus, for example, the drug may be dissolved or dispersed in the inert pharmaceutically acceptable solvent or oil.
- 15 The following is a simplified representation of the preparation of a cross-linked copolymer using the compound of formula I and glycerol:



acidic catalyst



Following administration of the compositions of this invention to the body, the drug is gradually released therefrom over a prolonged period and, at the same time, the copolymer is biodegraded to substances which can be readily disposed of by the body. As mentioned earlier, the copolymer is preferably one formed between the compound of formula I and a compound which occurs naturally in and/or is benign to the human body. Hydrolysis, especially acid hydrolysis, of such copolymers yields predominantly the latter compounds themselves. In the case of a copolymer prepared using glycerol as illustrated hereinbefore, the hydrolysis fragments of the compound of formula I are the following:



all of which are readily oxidisable for disposal by the body.

The rate of release of the drug from a composition provided by this invention can be controlled by a variety of methods.

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For example, in a copolymer prepared using given components the density of the cross-linking can be altered. Again, for example, the nature and amount of inert pharmaceutically acceptable solvent or oil which may be present in the  
5 composition can be varied.

A particular feature of compositions provided by the present invention which are based on cross-linked copolymers (i.e. matrices) is that such copolymers have a so-called glassy state (in which they are hard and brittle) and a rubber-like state,  
10 the change from the glassy state to the rubber-like state occurring at the so-called glass transition temperature. Following administration of such a composition having the copolymer in the glassy state the drug is gradually released and, at the same time, the copolymer is gradually biodegraded,  
15 this resulting in a gradual reduction of the glass transition temperature. When the glass transition temperature is reached the rubber-like state occurs and the copolymer becomes more rapidly biodegraded. Thus, if the glass transition temperature reaches body temperature, there is a rapid onset in the  
20 degradation. It will accordingly be evident that it is highly desirable to provide compositions based on cross-linked copolymers which initially have a glass transition temperature which lies somewhat above body temperature.

The compositions provided by the present invention may be  
25 administered for example by subcutaneous or intramuscular

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injection or implantation. In the case of forms for injection a composition of appropriate particle size can be dispersed in a pharmaceutically acceptable carrier material adapted for subcutaneous or intramuscular administration.

5 By appropriate choice of particle size and particle size distribution in the dispersant the rate of release of the drug can be controlled. Forms adapted for implantation include, for example, pellets, films, discs, rods and the like. Such implant forms can be prepared in a conventional

10 manner.

In many cases it is of advantage to include in the composition of the invention a combination of drugs to obtain most effective prophylaxis or treatment of a tropical disease.

The following Examples describe embodiments of the present

15 invention.

Example 1

The following ingredients were used to prepare a polymer matrix having a ratio of compound I to glycerol of 3:2 and containing 50% by weight of norethisterone:

|    |                                                                                    |          |
|----|------------------------------------------------------------------------------------|----------|
| 20 | Glycerol                                                                           | 215.5mg  |
|    | 3,4-Dihydro-2H-pyran-2-methyl-(3,4-dihydro-2H-pyran-2-carboxylate)<br>(Compound I) | 790.0 mg |
|    | Ferric chloride                                                                    | 10.0 mg  |
| 25 | Amodiaquine                                                                        | 53.4 mg. |

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A solution of the ferric chloride in the glycerol is warmed to 80°C and the compound I is added dropwise while warming and stirring between the additions. Compound I is initially incompatible with the glycerol, but by gradual  
5 additions and warming until the mixture becomes one phase, a stage is reached when the glycerol mixture will more readily accept the additions of compound I and become homogeneous.

After stoichiometric amounts of compound I to glycerol have been reached, the mixture is removed from the heating source  
10 and the amodiaquine is added to form a dispersion in the monomer mixture. A temperature of 80°C is maintained until polymerisation is complete and the desired polymer matrix is obtained containing 5% of amodiaquine by weight.

The dispersion referred to in the preceding paragraph can  
15 be used to prepare discs for implantation as follows:

Prior to the final polymerisation stage, the dispersion is spread on a film of Polythene, covered with a second film of Polythene and placed in a press which, when closed, leaves a gap between the Polythene films of the desired thickness for  
20 the copolymer matrix. A temperature of 80°C is applied until polymerisation is complete. The film of amodiaquine/polymer matrix is punched while still soft to produce flat discs and, after hardening has taken place, the Polythene backing is peeled off.

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Example 2

According to the procedure described in Example 1, the following ingredients were used to prepare a polymer matrix containing amodiaquine.

|   |                 |          |
|---|-----------------|----------|
| 5 | Glycerol        | 91.2 mg  |
|   | Compound I      | 332.9 mg |
|   | Ferric chloride | 42.4 mg  |
|   | Amodiaquine     | 93.3 mg  |

This produced a composition containing 20% by weight of amodiaquine dispersed in the polymer matrix.

Example 3

According to the method of Example 1, the following ingredients were used to prepare a composition comprising a dispersion of 25.8% of sulphamethizole in a polymer matrix.

|                 |          |
|-----------------|----------|
| Glycerol        | 215.5 mg |
| Compound I      | 790.0 mg |
| Ferric chloride | 10.0 mg  |
| Sulphamethizole | 262.0 mg |

EXAMPLE 4

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According to the method of Example 1, the following ingredients were used to prepare a polymer matrix containing cycloguanil

|   |                 |            |
|---|-----------------|------------|
| 5 | Glycerol        | 238mg      |
|   | Compound I      | 1,035.9 mg |
|   | Ferric chloride | 28 mg      |
|   | Cycloguanil     | 147 mg     |

The composition was worked-up as pellets for subcutaneous  
10 implantation 6mm in diameter and 2mm thick.

In tests on mice prolonged effectiveness against Plasmodium Bergei has been observed over periods in excess of three months.

EXAMPLE 5

15 According to the method of Example 1, the following ingredients were used to prepare a polymer matrix containing sulphadiazine (SDA)

|    |                 |          |           |
|----|-----------------|----------|-----------|
|    |                 | 10% SDA  | 30% SDA   |
|    | Glycerol        | 3054     | 4277 mg   |
|    | Compound I      | 1115.6   | 1561.1 mg |
| 20 | Ferric chloride | 3.1 mg   | 4.3 mg    |
|    | Sulphadiazine   | 165.2 mg | 854 mg    |

The composition was worked-up as a powder and as an implant of the same dimensions as in Example 4.

The powdered product was tested in powder form of particle  
25 size (a)  $< 53\mu$  and (b)  $53-96\mu$ . The powder (a) was suspended in glycerol and injected into the test mice: powder (b) was implanted. Prolonged protection in excess of five months of the test mice against the action of Plasmodium Bergei

has been observed.

EXAMPLE 6.

According to the method of Example 1, the following ingredients were used to prepare a polymer matrix  
5 containing pyrimethamine.

|                 |           |
|-----------------|-----------|
| Glycerol        | 3587 mg   |
| Compound I      | 1314.1 mg |
| Ferric chloride | 72 mg     |
| Pyrimethamine   | 716.9 mg  |

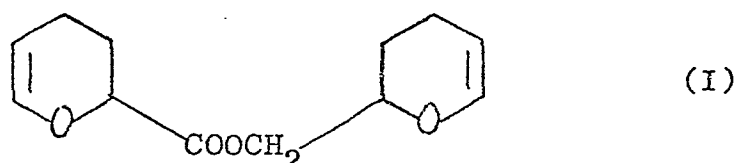
10 The product was formed into a pellet for subcutaneous implantation into test mice. The mice were protected against Plasmodium Berghei for periods in excess of three months



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## Claims:

1. A pharmaceutical composition comprising a drug which is an organic nitrogen compound of basic reaction and which is effective against a tropical disease, in admixture  
5 with a polymeric matrix of a copolymer of the compound of Formula I.



with at least one comonomer having more than one functional group selected from the group consisting of hydroxyl and carboxyl groups.

2. A pharmaceutical composition according to claim 1, in which the polymeric matrix is a copolymer of glycerol and the compound of Formula I defined in claim 1.
3. A pharmaceutical composition according to claim 2, in which the molar ratio of compound I to glycerol is 3:2.
4. A pharmaceutical composition according to claim 2 or 3, in which the copolymer is prepared under acid catalysis, the acidic catalyst being used in an amount sufficiently in excess of that required to neutralise the basic drug so as to catalyse the copolymerisation.

5. A pharmaceutical composition according to claim 4,  
in which the catalyst is ferric chloride.

6. A pharmaceutical composition of the following  
formulation:

|   |                 |                 |
|---|-----------------|-----------------|
| 5 | Glycerol        | 17% by weight   |
|   | Compound I      | 73.8% by weight |
|   | Ferric chloride | 0.2% by weight  |
|   | Cycloguanil     | 10% by weight   |

7. A pharmaceutical composition of the following  
10 formulation:

|                 |                 |
|-----------------|-----------------|
| Glycerol        | 20% by weight   |
| Compound I      | 69.8% by weight |
| Ferric chloride | 0.2% by weight  |
| Sulphadiazine   | 10% by weight   |

15 8. A pharmaceutical composition of the following  
formulation:

|                  |                 |
|------------------|-----------------|
| Glycerol         | 15% by weight   |
| Compound I       | 54.8% by weight |
| Ferric chloride  | 0.2% by weight  |
| 20 Sulphadiazine | 30% by weight   |

9. A pharmaceutical composition of the following  
formulation:

|                    |                 |
|--------------------|-----------------|
| Glycerol           | 15% by weight   |
| Compound I         | 54.7% by weight |
| 25 Ferric chloride | 0.3% by weight  |
| Pyrimethamine      | 30% by weight   |



| DOCUMENTS CONSIDERED TO BE RELEVANT                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                  | CLASSIFICATION OF THE APPLICATION (Int. Cl.)                                                                                                                                                                                                                                                                                |
|---------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Category                                                            | Citation of document with indication, where appropriate of relevant passages                                                                                                                                                                                                                                                                                                                                                                                                                                            | Relevant to claim                |                                                                                                                                                                                                                                                                                                                             |
|                                                                     | <p><u>FR - A - 2 260 356</u> (AMERICAN CYANAMID)</p> <p>* Page 1, lines 1-9; page 7, lines 1-4 *</p> <p>---</p> <p><u>US - A - 3 318 846</u> (SMITH et al.)</p> <p>* Column 1, line 16 - column 3, line 7; column 5, lines 21-75; column 7, lines 8-23; column 8, lines 4-14; column 9, lines 20-45; the claims *</p> <p>---</p> <p>THE MERCK INDEX, 8th edition, 1968,<br/>Merck &amp; Co. Rahway, N.J. USA</p> <p>* Page 310, "Cycloguanil", pages 892-893 "Pyrimethamine"; page 994 "Sulfadiazine". *</p> <p>---</p> | <p>1</p> <p>1-5</p> <p>1,6-9</p> | <p>A 61 K 9/26<br/>A 61 K 9/22<br/>C 08 G 65/34<br/>C 08 G 63/00</p> <p>TECHNICAL FIELDS SEARCHED (Int. Cl. 4)</p> <p>A 61 K 9/00<br/>A 61 K 9/22<br/>A 61 K 9/26<br/>C 08 G 65<br/>C 08 G 63</p>                                                                                                                           |
| P                                                                   | <p><u>FR - A - 2 336 936</u> (UNIVERSITY OF STRATHCLYDE)</p> <p>&amp; DE - A - 2 658 407 (UNIVERSITY OF STRATHCLYDE)</p> <p>* Page 1, line 1 - page 2, line 22; page 2, line 35 - page 7, line 16; the examples: the claims *</p> <p>---</p>                                                                                                                                                                                                                                                                            | 1-9                              |                                                                                                                                                                                                                                                                                                                             |
| A                                                                   | <p><u>CH - A - 428 234</u> (CIBA)</p> <p>----</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                  | <p>CATEGORY OF CITED DOCUMENTS</p> <p>X: particularly relevant<br/>A: technological background<br/>O: non-written disclosure<br/>P: intermediate document<br/>T: theory or principle underlying the invention<br/>E: conflicting application<br/>D: document cited in the application<br/>L: citation for other reasons</p> |
| <p>X The present search report has been drawn up for all claims</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                  | <p>&amp;: member of the same patent family,<br/>corresponding document</p>                                                                                                                                                                                                                                                  |
| Place of search                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                  | Date of completion of the search                                                                                                                                                                                                                                                                                            |
|                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                  | Examiner                                                                                                                                                                                                                                                                                                                    |