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ANTIMALARIAL COMPOSITION CONTAINING AN ACYLATED SULFONYLANILINE WITH TRIAZINE OR PYRIMIDINE SALT, AND METHOD OF USE

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6 Claims. (Cl. 167—65)

The present invention relates to repository therapeutic compositions useful in the treatment of malaria and to methods for the treatment of malaria by the use of these compositions.

More particularly, the present invention relates to repository antimalarial compositions comprising a sulfonylaniline compound in combination with one or more triazine salts or pyrimidine salts as set forth in greater detail below, and to methods for the preparation and use of such antimalarial compositions.

One of the objects of the present invention is to provide compositions for the treatment of malaria that are effective against both normal strains of malarial parasites and malarial parasites that have developed a resistance to or lessened sensitivity to drugs in clinical use such as chlorguanide, chlorproguanil, pyrimethamine, chloroquine, hydroxychloroquine, amodiaquine and p,p'-sulfonyldianiline.

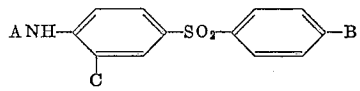
Another object of this invention is to provide compositions for the treatment of malaria wherein the compositions afford moieties that act synergistically over a wide range of doses and in a wide range of combinations.

A further object of this invention is to provide compositions for the treatment of malaria which afford moieties that greatly decrease the rate of emergence of resistance of malarial parasites to drugs.

Still another object of this invention is to provide compositions for the treatment of malaria which exhibit especially long duration of action, are non-irritating upon injection and are relatively non-toxic.

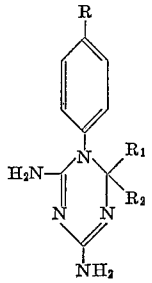
An additional object of this invention is to provide methods for the production and use of the compositions disclosed herein.

According to the invention, these as well as other objects are achieved by the production and use of pharmaceutical compositions comprising an acylated sulfonylaniline compound of the formula

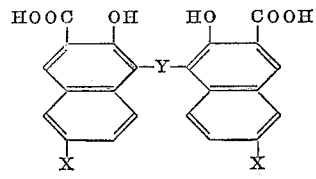


where A is an acyl group containing from 2 to 12 carbon atoms inclusive, B is an amino, acetamido or nitro group, and C is hydrogen or methyl, in combination with one or more triazine or pyrimidine salts as set forth below.

Specifically, the triazine salts employed in the compositions of the invention are salts of 4,6-diamino-1,2-dihydro-2-lower alkyl-1-aryl-s-triazines of the formula



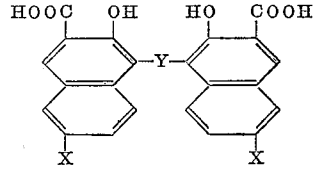
where R represents a chloro, iodo, methyl or benzyloxy radical, R_1 represents a lower alkyl radical and R_2 represents hydrogen or a methyl radical, with an acid of the formula



where Y represents a direct bond or methylene, benzylidene or thio and X represents hydrogen or bromine;

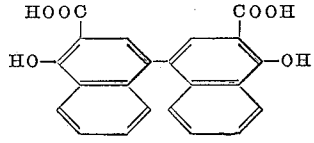
The pyrimidine salts employed in the compositions of the invention are 2,4-diamino-5-(p-chlorophenyl)-6-ethylpyrimidine salts with

(a) An acid of the formula

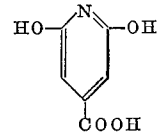


where Y represents a direct bond or methylene benzylidene or thio and X represents hydrogen or bromine;

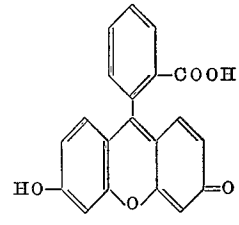
(b) An acid of the formula



(c) An acid of the formula

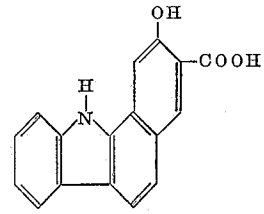


(d) An acid of the formula



or

(e) An acid of the formula



The compositions of the present invention are produced by formulating compositions comprising an acylated sulfonylaniline compound as defined above with one or more 4,6 - diamino-1,2-dihydro-2-lower alkyl-1-aryl-s-triazine salts or with one or more 2,4-diamino-1-(p-chlorophenyl)-6-ethylpyrimidine salts as defined above. Dosage unit forms for subcutaneous or intramuscular injection are

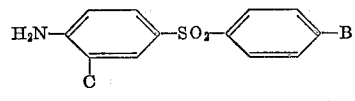
particularly suitable. For this purpose, the medicament can be incorporated with pharmacuetically-acceptable diluents. Both lipid and aqueous vehicles are suitable. Lipid vehicles suitable for use include vegetable oils such as castor oil, peanut oil, cottonseed oil, sesame oil, olive oil, expressed almond oil and the like, alone or in combination with benzyl benzoate and related compounds or with thickening agents known to the art such as aluminum monostearate. Agents suitable for incorporation in aqueous vehicles include polyvinylpyrrolidone, sodium carboxymethylcellulose, polyoxyethylene sorbitan monolaurate, benzethonium chloride, polyethylene glycol, sodium chloride and other adjuvants known to the art. The compositions may be dispensed in single or multiple dose ampoules or vials of various size or in disposable syringes or by instruments such as the Scherer Multidose Hypospray Jet Injector.

The percentages of the acylated sulfonylaniline compound and of the 4,6-diamino-1,2-dihydro-2-lower alkyl-1-aryl-s-triazine salts or 2,4-diamino-1-(p-chlorophenyl)-6-ethylpyrimidine salts in the compositions can be varied within wide limits, but in general the upper concentration limits of the medicaments are those that will afford a mixture that is syringable while the lower limits are the minimum amounts of the medicaments that will afford protection against malaria for a period of at least several months. For practical purposes, the medicaments are present in a concentration of 5% to 30%. The ratio of the acylated sulfonylaniline to the 4,6-diamino-1,2-dihydro-2-lower alkyl-1-aryl-s-triazine salt or 2,4-diamino-1-(p-chlorophenyl)-6-ethylpyrimidine salt will usually range from 1:10 to 10:1, but a ratio of about 1:1 is preferred.

According to the methods of this invention, the aforementioned compositions are administered in dosage unit form for the treatment and prophylaxis of malaria. The compositions are normally administered subcutaneously or intramuscularly, with the dose adjusted to the needs and tolerances of the individual patient. The dosages of the 4,6-diamino-1,2-dihydro-2-lower alkyl-1-aryl-s-triazine salts and the 2,4-diamino-5-(p-chlorophenyl)-6-ethylpyrimidine salts are conveniently expressed in terms of the free base equivalent whereas the dosages of the acylated sulfonylaniline compounds are expressed in terms of total drug. The composition is usually administered in a single dose within the range of approximately 25 mg. to 2000 mg. or 2.5 mg./kg. to 20 mg./kg. per patient quarterly, semi-annually or annually, these weights representing total active ingredients with the triazine or pyrimidine salt being calculated as free base equivalent. Within the indicated range, the dose is adjusted according to the size and age of the patient and the patient's response to medication. For example, in the case of a child the proper dose would commonly be found near the lower limit of the indicated range whereas in the case of an adult experiencing no side-effects, the proper dose would commonly be found near the upper limit of the indicated range.

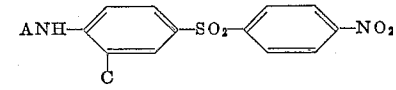
The triazine and pyrimidine salts employed in the compositions of the invention can be prepared by reacting a corresponding soluble triazine or pyrimidine salt such as the hydrochloride with a soluble salt of one of the designated acids such as the sodium salt, or as described more fully in co-pending applications Serial Nos. 83,909, now U.S. Patent No. 3,074,947; 83,910; 188,984, now U.S. Patent No. 3,161,641; and 188,985.

The acylated sulfonylaniline compounds employed in the compositions of the invention can be prepared by reacting a compound of the formula



with the appropriate acyl halide in pyridine or with an

acid anhydride in acetic acid; or by the reduction of a compound of the formula



where A, B and C are as defined before.

The compositions and methods of the invention are of value in the treatment and prophylaxis of malaria, having the advantages of prolonged duration of action, unexpectedly high chemotherapeutic activity, decreased emergence of resistant strains, and good pharmaceutical acceptability.

Malaria is a disease of great medical and economic importance in many areas of the world, particularly in tropical and semi-tropical climates. The great number and variety of therapeutic agents which have been proposed for the treatment of malaria reflect the difficulties which have been encountered in developing satisfactory means for the treatment and control of this disease. In spite of eradication or impressive control in some areas, malaria still annually affects 200 million people and causes one million deaths. Interruption of transmission and elimination of malaria by the use of antimalarial drugs depends primarily on the constant maintenance of an effective schizontocidal concentration of the drug in the blood of every individual in an affected community. Two major needs hinder the solution of this problem. First, in view of the difficulties of mass administration in many parts of the world there is a need for a schizontocide and sporontocide with prolonged action, so that a single dose of it would maintain its activity for several months or longer. Second, there is a need for the development of an antimalarial agent that would be effective against strains of malarial parasites that have become resistant to the drugs in common use and that would prevent or retard the emergence of drug resistance in the future.

Among the antimalarial drugs in current use, none exhibits prolonged action. Thus, drugs such as chlorguanide, chlorproguanil, pyrimethamine, p,p'-sulfonyldianiline, chloroquine, hydroxychloroquine and amodiaquine must be given daily or weekly if complete interruption of transmission is to be achieved. Further, compounds such as 4,6-diamino-1-(p-chlorophenyl)-1,2-dihydro-2,2-dimethyl-s-triazine hydrochloride are very rapidly excreted and because of this are of limited value as antimalarial agents. Observations of lessened sensitivity of malarial parasites to many types of antimalarial drugs have been reported, including pyrimethamine, chlorguanide, chlorproguanil, chloroquine, hydroxychloroquine, amodiaquine, quinine, pamaquine and quinacrine.

Various insoluble salts of 4,6-diamino-1,2-dihydro-2-lower alkyl-1-aryl-s-triazine and 2,4-diamino-5-(p-chlorophenyl)-6-ethylpyrimidine exhibit prolonged antimalarial action and are non-irritating upon injection. However, strains of malarial parasites that are known to be resistant to chlorguanide, pyrimethamine and 4,6-diamino-1-(p-chlorophenyl)-1,2-dihydro-2,2-dimethyl-s-triazine hydrochloride are also less susceptible to these compounds.

Although p,p'-sulfonyldianiline is known to have antimalarial activity, it does not exhibit prolonged antimalarial action. In accordance with the present invention, it has now been found that acylated sulfonylaniline compounds employed in the compositions and methods of the invention possess prolonged antimalarial activity of especially long duration and are non-irritating upon injection. The components present in the compositions of the invention exhibit enhanced activity in combination, producing unexpectedly high antimalarial activity of prolonged duration with greatly decreased emergence of resistant strains of malarial parasites.

For reasons of optimal activity, pharmaceutical ac-

ceptability, and low cost, the preferred salts for use in the compositions of the invention are the designated triazine salts. The preferred acylated sulfonylaniline compound is p,p'-sulfonylbis(acetanilide), otherwise known as p,p'-bis(acetamido)diphenyl sulfone. The preferred composition of the invention is the 4,6-diamino-1-(p-chlorophenyl)-1,2-dihydro-2,2-dimethyl-s-triazine salt with one-half formula weight 4,4'-methylenebis-(3-hydroxy-2-naphthoic acid) in combination with p,p'-sulfonylbis(acetanilide). The preferred product form is an aqueous suspension for parenteral administration.

The invention is illustrated by the following examples. In these examples quantities of the triazine and pyrimidine salts are expressed in terms of the free base equivalents whereas quantities of all other ingredients are expressed as actual weights or volumes.

Example 1

	Mg.
4,6-diamino-1-(p-chlorophenyl)-1,2-dihydro-2,2-dimethyl-s-triazine salt with ½ formula weight 4,4'-methylenebis(3-hydroxy-2-naphthoic acid)	[1] 75
p,p'-Sulfonylbis(acetanilide)	75
Polyvinylpyrrolidone	0.5
Sodium carboxymethyl cellulose	5.0
Polyoxyethylene sorbitan monolaurate	0.01
Benzethonium chloride	0.1
Water for injection, to make 1 ml.	

[1] Base equivalent.

The polyvinylpyrrolidone, sodium carboxymethyl cellulose, polyoxyethylene sorbitan monolaurate and benzethonium chloride are dissolved in the water for injection. This solution is autoclaved at 120° C. for 30 minutes at 15 pounds per square inch pressure. The 4,6-diamino-1-(p-chlorophenyl)-1,2-dihydro-2,2-dimethyl-s-triazine salt with ½ formula weight 4,4'-methylenebis(3-hydroxy-2-naphthoic acid) and p,p'-sulfonylbis(acetanilide) are heat sterilized at 160° C. for 2 hours. After cooling to room temperature, these ingredients are aseptically suspended in the aqueous vehicle. The suspension is dispensed in 5 ml. portions into glass bottles.

Example 2

	Mg.
4,6-diamino-1-(p-chlorophenyl)-1,2-dihydro-2,2-dimethyl-s-triazine salt with ½ formula weight 4,4'-methylenebis(3-hydroxy-2-naphthoic acid)	[1] 75
p,p'-Sulfonylbis(acetanilide)	75
Benzyl benzoate 40%, castor oil 60%, to make 1 ml.	

[1] Base equivalent.

The castor oil and benzyl benzoate are mixed and passed through a coarse sintered glass filter. The other ingredients are added to the vehicle and the resulting mixture is stirred. The suspension is dispensed into 5 ml. ampoules which are then sealed and sterilized by autoclaving at 120° C. for 30 minutes.

Example 3

4,6-diamino-1-(p-chlorophenyl)-1,2-dihydro-2,2-dimethyl-s-triazine salt with ½ formula weight 4,4'-methylenebis(3-hydroxy-2-naphthoic acid) ____mg__	[1] 150
4'-(N-acetylsulfanilyl)propionanilide ____mg__	150
Benzethonium chloride ____mg__	0.1
Polyoxyethylene sorbitan monolaurate ____mg__	0.1
Polyvinylpyrrolidone ____mg__	0.5
Sodium carboxymethyl cellulose ____mg__	2.5
Polyethyleneglycol, average molecular weight 3000 to 3700 ____ml__	0.3
Sodium chloride ____mg__	9
Water for injection, to make 1 ml.	

[1] Base equivalent.

The benzethonium chloride, polyoxyethylene sorbitan monolaurate, polyvinylpyrrolidone, sodium carboxymethyl cellulose, polyethyleneglycol and the sodium chloride are dissolved in the water for injection. This solution is autoclaved at 120° C. for 30 minutes. The 4,6-diamino-1-(p-chlorophenyl)-1,2-dihydro-2,2-dimethyl-s-triazine salt with ½ formula weight 4,4'-methylenebis(3-hydroxy-2-naphthoic acid) and the 4'-(N-acetylsulfanilyl)propionanilide are heat sterilized at 160° C. for 2 hours, cooled to room temperature, and suspended in the aqueous vehicle. The suspension is dispensed in 5 ml. portions into glass bottles.

Example 4

	Mg.
4,6-diamino-1-(p-chlorophenyl)-1,2-dihydro-2,2-dimethyl-s-triazine salt with ½ formula weight 4,4'-methylenebis(3-hydroxy-2-naphthoic acid)	[1] 25
p,p'-Sulfonylbis(acetanilide)	25
Polyvinylpyrrolidone	0.25
Sodium carboxymethyl cellulose	10
Polyoxyethylene sorbitan monolaurate	0.005
Benzethonium chloride	0.1
Water for injection, to make 1 ml.	

[1] Base equivalent.

The ingredients are formulated in the same manner as described in Example 1.

Example 5

	Mg.
4,6-diamino-1,2-dihydro-2,2-dimethyl-1-p-tolyl-s-triazine salt with ½ formula weight 4,4'-methylenebis(3-hydroxy-2-naphthoic acid)	[1] 50
4'-(N-acetylsulfanilyl)propionanilide	50
Polyvinylpyrrolidone	1.0
Sodium carboxymethyl cellulose	5.0
Polyoxyethylene sorbitan monolaurate	0.01
Benzethonium chloride	0.1
Water for injection, to make 1 ml.	

[1] Base equivalent.

The ingredients are formulated in the same manner as described in Example 1.

Example 6

	Mg.
4,6-diamino-1,2-dihydro-1-(p-iodophenyl)-2,2-dimethyl-s-triazine salt with ½ formula weight 4,4'-methylenebis-(3-hydroxy-2-naphthoic acid)	[1] 75
p-Sulfanilyllauranilide	75
Aluminum monostearate	20
Castor oil, to make 1 ml.	

[1] Base equivalent.

The castor oil and aluminum monostearate are mixed together and heated until a vehicle of satisfactory consistency is obtained. The other ingredients are suspended in the vehicle. The suspension is dispensed in 5 ml. portions into 7 ml. ampoules which are then sealed and sterilized by autoclaving at 120° C. for 30 minutes.

[1] Base equivalent.

Example 7

	Mg.
4,6-diamino-1-[p-(benzyloxy)phenyl]-1,2-dihydro-2,2-dimethyl-s-triazine salt with ½ formula weight 4,4'-methylenebis(3-hydroxy-2-naphthoic acid)	[1] 50
3'-methyl-4',4'''-sulfonylbis(acetanilide)	50
Polyvinylpyrrolidone	0.5
Sodium carboxymethyl cellulose	7.5
Polyoxyethylene sorbitan monolaurate	0.01
Benzethonium chloride	0.1
Water for injection, to make 1 ml.	

[1] Base equivalent.

The ingredients are formulated in the same manner as described in Example 1.

3'-methyl-4',4'''-sulfonylbis(acetanilide), employed as a starting material in the above procedure, can be prepared as follows: A mixture of 34.6 g. of 4,4'-diamino-3-methyldiphenyl sulfone, 100 ml. of glacial acetic acid and 34 g. of acetic anhydride is stirred and boiled under reflux for 2 hours. Upon cooling, the colorless crystals are collected by filtration and washed successively with water, ethanol and ether; M.P. 256–258° C.

Example 8

	Mg.
4,6-diamino - 1,2 - dihydro-1-(p-iodophenyl)-2,2-dimethyl-s-triazine salt with ½ formula weight 4,4'-thiobis(3-hydroxy-2-naphthoic acid)	[1] 25
4'-(N-acetylsulfanilyl)hexanilide	75

[1] Base equivalent.

The vehicle is prepared and the ingredients are formulated as in Example 7.

Example 9

	Mg.
4,6 - diamino - 1 - (p - chlorophenyl) - 2 - ethyl - 1,2-dihydro-s-triazine salt with ½ formula weight 4,4' - benzylidenebis - (3 - hydroxy - 2 - naphthoic acid)	[1] 75
p-(p-Nitrophenylsulfonyl)acetanilide	150

[1] Base equivalent.

The vehicle is prepared and the ingredients are formulated as in Example 2.

Example 10

	Mg.
4,6 - diamino - 1,2 - dihydro - 1 - (p-iodophenyl) - 2,2 - dimethyl - s - triazine salt with ½ formula weight 4,4'-methylenebis(7-bromo-3-hydroxy-2-naphthoic acid)	[1] 150
4' - (p - Acetamidophenylsulfonyl)dodecananilide	50

[1] Base equivalent.

The vehicle is prepared and the ingredients are formulated as in Example 7.

Example 11

	Mg.
2,4 - diamino - 5 - (p - chlorophenyl) - 6 - ethyl - pyrimidine salt with ½ formula weight 4,4'-methylenebis(3-hydroxy-2-naphthoic acid)	[1] 150
p,p'-Sulfonylbis(acetanilide)	100

[1] Base equivalent.

The vehicle is prepared and the ingredients are formulated as in Example 2.

Example 12

	Mg.
2,4 - diamino - 5 - (p - chlorophenyl) - 6 - ethyl - pyrimidine salt with 1 formula weight 2,6-dihydroxyisonicotinic acid	[1] 100
4' - Sulfanilylacetanilide	100

[1] Base equivalent.

The vehicle is prepared and the ingredients are formulated as in Example 2.

Example 13

	Mg.
2,4 - diamino - 5 - (p - chlorophenyl) - 6 - ethyl - pyrimidine salt with ½ formula weight 4,4'-dihydroxy(1,1' - binaphthalene) - 3,3' - dicarboxylic acid	[1] 25
p-Sulfanilyllauranilide	25

[1] Base equivalent.

The vehicle is prepared and the ingredients are formulated as in Example 2.

Example 14

	Mg.
2,4 - diamino - 5 - (p - chlorophenyl) - 6 - ethyl - pyrimidine salt with ½ formula weight, 6,6'-dibromo - 2,2' - dihydroxy - (1,1' - binaphthalene) - 3,3'-dicarboxylic acid	[1] 25
3'-methyl-4',4'''-sulfonylbis(acetanilide)	250
Benzethonium chloride	0.1
Polyoxyethylene sorbitan monolaurate	0.1
Sodium carboxymethyl cellulose	2.5
Water for injection, to make 1 ml.	

[1] Base equivalent.

The ingredients are formulated in the same manner as described in Example 1.

Example 15

	Mg.
2,4 - diamino - 5 - (p - chlorophenyl) - 6 - ethyl - pyrimidine salt with ½ formula weight 4,4'-methylenebis(7 - bromo - 3 - hydroxy - 2 - naphthoic acid)	[1] 250
4'-(N-acetylsulfanilyl)propionanilide	25

[1] Base equivalent.

The vehicle is prepared and the ingredients are formulated as in Example 2.

Example 16

	Mg.
2,4 - diamino - 5 - (p - chlorophenyl) - 6 - ethyl - pyrimidine salt with 1 formula weight fluorescein	[1] 75
4'-(N-acetylsulfanilyl)hexanilide	75

[1] Base equivalent.

The vehicle is prepared and the ingredients are formulated as in Example 1.

Example 17

	Mg.
2,4 - diamono - 5 - (p - chlorophenyl) - 6 - ethyl - pyrimidine salt with 1 formula weight 2-hydroxy-11H-benzo[a]carbazole-3-carboxylic acid	[1] 50
4' - (p - acetamidophenylsulfonyl)dodecananilide	50
Polyvinylpyrrolidone	1.0
Sodium carboxymethyl cellulose	7.5
Polyoxyethylene sorbitan monolaurate	0.01
Benzethonium chloride	0.1
Water for injection, to make 1 ml.	

[1] Base equivalent.

The ingredients are formulated in the same manner as described in Example 1.

Example 18

	Mg.
4, 6 - diamino - 1 -(p - chlorophenyl)- 1,2 - dihydro - 2,2-dimethyl-s-triazine salt with ½ formula weight 4,4' - methylenebis(3-hydroxy-2-naphthoic acid)	[1] 50
2,4 - diamino - 5 - (p - chlorophenyl) - 6 - ethyl pyrimidine salt with ½ formula weight 6,6'-dibromo - 2,2' - dihydroxy - (1,1' - binaphthalene) - 3,3'-dicarboxylic acid	[1] 50
p,p'-Sulfonylbis(acetanilide)	50

[1] Base equivalent.

The vehicle is prepared and the ingredients are formulated as in Example 1.

Example 19

	Milligram
4,6 - diamino - 1 - (p - chlorophenyl) - 1,2 - dihydro - 2,2-dimethyl-s-triazine salt with ½ formula weight 4,4' - methylenebis(3 - hydroxy - 2 - naphthoic acid)	[1] 50
4'-(N-acetylsulfanilyl)propionanilide	50
p-Sulfanilyllauranilide	50

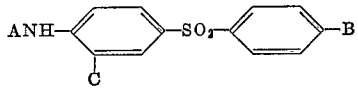
[1] Base equivalent.

The vehicle is prepared and the ingredients are formulated as in Example 2.

We claim:

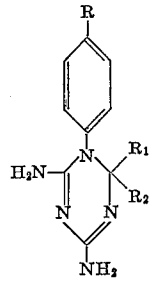
1. A repository antimalarial composition comprising a pharmaceutically-acceptable carrier and, in combination, 1 part by weight of an acylated sulfonylaniline compound and 0.1 to 10 parts by weight calculated as free base equivalent, of a member of the class consisting of triazine salts and pyrimidine salts;

said acylated sulfonylaniline compound being a compound of the formula

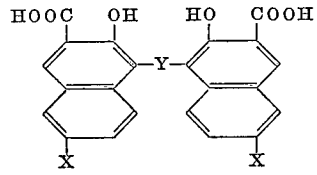


where A is an unsubstituted acyl having from 2 to 12 carbon atoms inclusive, B is selected from the class consisting of amino, acetamido and nitro, and C is selected from the class consisting of hydrogen and methyl;

said triazine salts being salts of 4,6-diamino-1,2-dihydro-2-lower alkyl-1-aryl-s-triazines of the formula



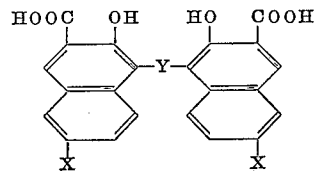
where R is selected from the class consisting of chloro, iodo, methyl and benzyloxy, R_1 is lower alkyl and R_2 is selected from the class consisting of hydrogen and methyl, with an acid of the formula



where Y is selected from the class consisting of a direct bond, methylene, benzylidene and thio and X is selected from the class consisting of hydrogen and bromine;

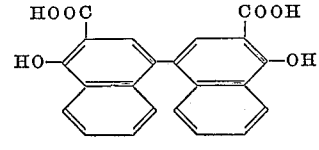
said pyrimidine salts being salts of 2,4-diamino-5-(p-chlorophenyl)-6-ethylpyrimidine with a member of the class consisting of

(a) an acid of the formula

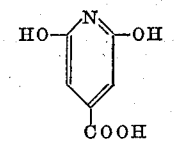


where Y is selected from the class consisting of a direct bond, methylene, benzylidene and thio and X is selected from the class consisting of hydrogen and bromine;

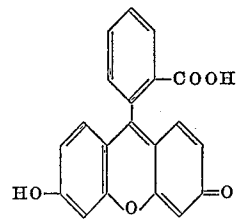
(b) an acid of the formula



(c) an acid of the formula

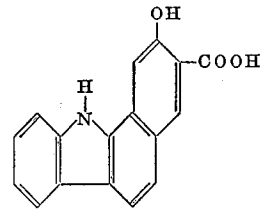


(d) an acid of the formula



and

(e) an acid of the formula



2. A repository antimalarial composition comprising a pharmaceutically-acceptable carrier and, in combination, 1 part by weight of p,p'-sulfonylbis(acetanilide) and 0.1 to 10 parts by weight calculated as free base equivalent, of 4,6-diamino - 1 - (p-chlorophenyl) - 1,2-dihydro-2,2-dimethyl-s-triazine salt with one-half formula weight 4,4'-methylenebis(3-hydroxy-2-naphthoic acid).

3. A repository antimalarial composition comprising, in combination, 1 part by weight of p,p'-sulfonylbis(acetanilide) and 0.1 to 10 parts by weight calculated as free base equivalent, of 4,6-diamino - 1 - (p-chlorophenyl)-1,2-dihydro-2,2-dimethyl-s-triazine salt with one-half formula weight 4,4'-methylenebis(3 - hydroxy - 2 - naphthoic acid) dispersed in a pharmaceutically-acceptable lipid vehicle for parenteral administration.

4. A repository antimalarial composition comprising, in combination, 1 part by weight of p,p'-sulfonylbis(acetanilide) and 0.1 to 10 parts by weight calculated as free base equivalent, of 4,6-diamino - 1 - (p-chlorophenyl)-1,2-dihydro-2,2-dimethyl-s-triazine salt with one-half formula weight 4,4'-methylenebis(3 - hydroxy - 2 - naphthoic acid) dispersed in an aqueous vehicle for parenteral administration.

5. A method for the treatment and prophylaxis of malaria which comprises administering a repository antimalarial composition as defined in claim 1 to a human being.

6. A method for the treatment and prophylaxis of malaria which comprises parenterally administering to a human being a repository antimalarial composition comprising a pharmaceutically-acceptable carrier and, in combination, 1 part by weight of p,p'-sulfonylbis(acetanilide) and 0.1 to 10 parts by weight calculated as free base equivalent, of 4,6-diamino - 1-(p-chlorophenyl)-1,2-dihydro-2,2 - dimethyl - s - triazine salt with one-half formula weight 4,4'-methylenebis(3-hydroxy-2-naphthoic acid).

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