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(6) CHEMOTHERAPY OF RODENT MALARIA
EVALUATION OF DRUG ACTION AGAINST NORMAL AND RESISTANT STRAINS, INCLUDING EXO-ERYTHROCYTIC STAGES,

(9) FINAL TECHNICAL REPORT, 31 Oct 75 – 31 Dec 76,

by

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Data are provided on the blood schizontocidal action of 8 WRAIR compounds and the tissue schizontocidal activity of a total of 110 WRAIR 8-aminoquinolines plus 29 other compounds. Emphasis is laid on the comparison of a new series of 5-substituted 8-aminoquinolines and comparison has been made between data obtained in our rodent models and reports on work in simian models from other investigators. A good parallel was found with tissue schizontocidal activity.

The administration of mixtures of mefloquine with pyrimethamine, sulphaphenazole or ~~>

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primaquine has been shown to enhance the development of resistance by P. berghei to the individual components.

Studies have continued on the modes of action of mefloquine, chloroquine and quinine. Mefloquine has been shown to have relatively little effect on the uptake of adenosine. The synergistic action of chloroquine and erythromycin against chloroquine-resistant parasites has been further investigated. The mechanism of this synergism is still obscure. Other work has involved the study of electron transport and cathepsins of rodent malaria parasites.

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TABLE OF CONTENTS

1. INTRODUCTION

In this Report we review work carried out between the termination of our last contract on 31 October 1975 through 31 December, 1976. Details of this work have been provided in Quarterly Reports Numbers 1 through 3.

The main emphasis of this year's studies has been the evaluation in depth of the causal prophylactic potential of new WR compounds and a comparison of the data obtained in our rodent malaria screen with that of Dr. Leon Schmidt's rhesus-*P. cynomolgi* system[1].

Another major item of our programme has been the follow-up of studies to evaluate the effect of polytherapy in reducing the rate at which *P. berghei* develops resistance to mefloquine. Details of this study are now ready for publication and summaries are included in the following pages.

Further studies have been made on the effect of several compounds against the sporogonic stages of rodent malaria, and on the fundamental biochemical processes of the blood stages, especially glycolysis.

2. CYCLICAL PASSAGE OF RODENT MALARIA STRAINS

We have continued to rely on the *P. yoelii nigeriensis*-*Anopheles stephensi* combination for the supply of infected mosquitoes for chemotherapy investigations. A temporary falloff in oocyst development was finally traced down to fluctuations in the temperature of the insectary due to a defective thermostat. Replacement of this has brought our cyclical transmission back to normal levels.

3. PRODUCTION OF DRUG-RESISTANT LINES

3.1 NS-type lines of *P. berghei*

After several years of research and soul-seeking we have been able to reach the conclusion that several strains of *P. berghei* from highland areas of the Katanga region of Zaire are in fact a mixture of two species. The importance of this will be appreciated when it is pointed out that one of the mixture, *P. berghei sensu stricto*, is chloroquine sensitive, and the other which we call "*P. yoelii* ssp." is innately chloroquine-resistant. These conclusions must influence our interpretation of all work carried out up to now on isolates of rodent malaria from this part of Africa. The following is the summary of a paper now submitted for publication on this topic[2].

'Under chloroquine selection pressure a number of chloroquine-resistant lines of rodent malaria have been selected from "strains" of "*P. berghei*" originating in the Katanga highlands. They are called the "NS lines". No resistant parasite was obtained from a clone under drug pressure, nor from two other highland *P. berghei* and a strain of *P. v. vinckei*.

The isoenzyme typing of these parasites indicates that the drug-resistant NS parasites are allied to P. yoelii rather than P. berghei, but that they can be distinguished from all but the subspecies P. y. nigeriensis, sharing with this GPI 2, 6PGD 4, LDH11 and GDH 2. The resistant organism is therefore labelled P. yoelii ssp.

The buoyant density of all P. berghei and P. yoelii subspecies examined is identical (1.683 g/ml). DNA-DNA hybridisation studies have shown that P. yoelii ssp. differs significantly not only from P. berghei, but also from P. y. yoelii and P. y. nigeriensis in terms of the base sequence homologies of these parasites.

Cross-immunity experiments indicate that P. yoelii ssp. differs not only from P. berghei, but also from P. y. nigeriensis in the absence of reciprocal cross-protection, although P. berghei itself (as well as the mixtures containing P. yoelii ssp.) provide a broad and relatively non-specific protection against the other parasites.

Evidence is presented to refute the suggestion that the "NS lines" have become accidentally mixed with P. berghei in the laboratory. On the contrary, the evidence indicates that the NS lines are not P. y. nigeriensis but a new subspecies in the P. yoelii complex. How such mixtures of P. berghei and P. yoelii ssp. have survived through many years and countless syringe passages in the laboratory is unknown, but this is not an isolated instance in the history of the rodent malarias. The existence of P. yoelii ssp. may account for a number of previously unaccountable observations in the laboratory such as some of the apparent "variability" of P. berghei "strains" under a variety of experimental conditions.

The importance of these findings is discussed in relation to the zoogeography of the rodent malarias.'

3.2 Polytherapy in the prevention of drug-resistance

We have already reported the relative ease with which resistance can be developed to mefloquine, and preliminary data on our attempts to decrease the rate at which this resistance develops through the use of drug mixtures. Using a relapse technique resistance of P. berghei N strain to mefloquine can be developed slowly (Fig. 1), but the progress is more rapid in the chloroquine-resistant NS lines. Mefloquine resistance in all these lines is very unstable in the absence of drug selection pressure (Fig. 2).

Resistance develops also when the N strain is submitted to slowly increasing mefloquine dosage in consecutive passages (Fig. 3), the resulting parasites having a similar morphology at light microscope level to chloroquine-resistant P. berghei RC line parasites. Like the latter they occupy polychromatophilic red blood cells almost exclusively.

When the parasites are exposed to mixtures of mefloquine with pyrimethamine, sulphaphenazole or primaquine, resistance to each component of the mixtures develops more slowly than to the individual components used alone (Figs. 4 to 6).

It is strongly recommended that mefloquine should only be deployed for the prevention of treatment of malaria in man caused by chloroquine-resistant P. falciparum. For large-scale use mefloquine should not be employed until a second antimalarial has been identified that will minimise the risk of parasites becoming resistant to this potentially valuable new compound.

A full report on this work has been submitted for publication[3].

4. CHEMOTHERAPY STUDIES

4.1 Blood schizontocides

4.1.1 New compounds

The evaluation of new compounds for blood schizontocidal activity has been restricted to some 8 compounds on which data were provided in our 3rd Quarterly Report. Three compounds showed good activity against the drug-sensitive N strain of P. berghei, namely WR 219,930, 194,965, and 225,449, the last two being somewhat more effective po than sc. No studies were made in drug-resistant lines with these compounds.

4.1.2 Drug combinations

The main purpose of our drug combination work this year was to determine whether those combinations with mefloquine that we have shown to reduce the rate of resistance development possessed additive or even potentiating properties. The details were given in our 3rd Quarterly Report and are to be published[4].

The data summarised in Fig. 7 indicate that there is certainly no potentiation between mefloquine and primaquine, or mefloquine and sulphaphenazole. There is a slight indication of potentiation between mefloquine and pyrimethamine but possibly only of the order that could be anticipated if the two compounds influence each other's pharmacokinetics in the host.

4 2 Causal prophylaxis- the value of the rodent screen

The greater part of our work has been devoted to examining the causal prophylactic potential of new WR compounds in our rodent malaria model. We have examined altogether some 110 WRAIR 8-aminoquinolines plus 5 from other sources, 6 naphthyridines and 18 miscellaneous compounds that are covered in the present report. Other miscellaneous compounds have been dealt with in previous Quarterly and Final Reports over the years.

We have presented these data in tabular form (Tables 1 through 14) and in these we include our own interpretation of Minimum Fully Curative Doses (MCFD) presented in Schmidt's Final Report of 1976. The figures we give for the MCFD values take into account dose levels at which cure was obtained only in some animals but not in all treated at any particular level, and the values are converted to uM base/kg. In our rodent model animals were routinely treated on a single occasion, by the sc route and it is only recently that we have started to use also the oral route. For this reason there are still many blanks in Tables 1 through 14 that we will be filling in on the basis of ongoing studies. This makes a direct comparison of the 145 compounds that both we and Schmidt have examined difficult at the present time. As we have pointed out previously it is, in a way, surprising that there should be any correlation between our data. Schmidt uses a different parasite, different host, different route of administration and different dosage schedule from ourselves. Nevertheless on the basis of the primaquine indices as we have calculated them so far we find a remarkably good correlation between our data in the majority of the 8-aminoquinolines series.

There is however one important area in which we differ considerably and that is the area represented by poorly soluble and (probably) poorly orally absorbable compounds such as menoctone (WR 49,808) and WR 226,626. This type of compound we believe to be extremely interesting since those members that we have examined have proved to possess not only tissue schizontocidal properties but also good activity against both drug-sensitive and drug-resistant blood stages of P. berghei. In this sense we believe that the rodent malaria screen offers advantages over the rhesus-P. cynomolgi screen. While appreciating the great value of the simian model we do feel that many important leads may be missed if total reliance is placed on this and that the rodent screen has a most valuable contribution to make as we have indicated elsewhere[5].

Data on compounds still receiving preliminary screening are presented in Table 15 through 38, while completed sheets not yet forwarded to WRAIR form Tables 39 through 53.

4.3 Sustained release of drugs

The work on the sustained release of antimalarials from poly-dimethylsiloxane capsules reported in the 3rd Quarterly Report 1976 (2.4) has been continued and expanded. To date pyrimethamine filled capsules having a wall thickness of 0.63 mm and an internal surface area of 105 sq. mm. have afforded complete protection to mice against P. berghei (N strain) challenge for a period of 102 days. Capsules with an internal surface area of approximately 25 sq. mm. gave mice a survival time of between 55 and 65 days though all mice had patent parasitaemias from approximately day+38 onwards. Very similar results were obtained with capsules having an internal surface area of approximately 50 sq. mm.

No antimalarial effect was observed with encapsulated cycloguanil, WR 99209 and WR 99210. Promising preliminary results have been obtained with another cycloguanil analogue and menoctone and these compounds are being studied in greater detail.

Current experiments are designed to utilise drug capsules prepared by mixing drug and pre-vulcanised silastic as described by Fu et al.[6] and drug incorporated into biodegradable polymers.

4.4 Mode of drug action

4.4.1 Chloroquine and mefloquine

The method by which chloroquine kills the malaria parasite is still not known. Its short-term effect in causing the clumping of haemozoin has been investigated in considerable depth, but haemozoin clumping itself does not kill the parasite. We are therefore investigating the time at which the parasite dies after treatment with chloroquine and the way in which the action of mefloquine differs from that of chloroquine.

The clumping of malaria pigment by chloroquine (10^{-6}M) is complete within 80 minutes but there is no effect within this time on growth of the parasite, as measured by the incorporation of radio-active adenosine. Six hours after treatment of P. berghei-infected mice with chloroquine (60 mg/kg) incorporation of adenosine was reduced by about 25%, but after 12 hours the synthesis of nucleic acids had fallen sharply. These results suggest that P. berghei dies only after about 12 hours exposure to chloroquine and closely parallel those obtained by Davies and Howells (unpublished) in experiments on the viability of the parasite after varying times of exposure in vivo to chloroquine. Radioactive chloroquine taken up by P. berghei parasitized cells maintains its maximum intracellular concentration for at least three hours in vitro. It seems that the clumping of haemozoin is unrelated to the death of the parasite.

The effect of mefloquine on the erythrocytic stages of P. berghei has been reexamined at the light and electron microscope levels. The most obvious effects of the compound were observed in the haemozoin vesicles of the parasite, with the ultrastructural changes being broadly similar to those described in P. berghei treated with WR 122455 and quinine[7]. Within 3 hours of exposure to a single subcutaneous dose of 60 mgm/kg primary pigment clumps are formed, but not autophagosomes. With longer periods of exposure to the compound pigment grains became increasingly finer and electron translucent, with only poorly defined haemozoin grains being found in trophozoites 24 hours after treatment. These observations amplify the very slow plasmodicidal action of this compound and suggest that the drug is not solubilizing haemozoin, as was suggested for WR 122455 and quinine by Davies et al.[7] but interferes with the catabolism of haemoglobin and/or the formation of haemozoin. Mefloquine (10^{-5}M) only slightly reduced the incorporation of adenosine by parasitized cells in one hour. A detailed study is proceeding.

4.4.2 Chloroquine and erythromycin

The synergistic action of erythromycin and chloroquine on chloroquine-resistant parasites does not appear to be due to an increased uptake of chloroquine in the presence of the antibiotic. In vitro, slightly more chloroquine was taken up by RC strain P. berghei in the presence of erythromycin but treatment of infected mice with erythromycin before measurement of chloroquine uptake in vitro, dramatically reduced the uptake of chloroquine.

No obvious effects on the ultrastructure of P. berghei (N strain) were observed following treatment with erythromycin. Studies are in progress on the effects of chloroquine and erythromycin, alone and in combination, on the RC strain P. berghei.

4.4.3 Pyrimethamine

The effects of pyrimethamine on the erythrocytic stages of P. berghei have been examined at the electron microscope level. These effects were described in the 3rd Quarterly Report of 1976.

5. PHYSIOLOGY AND BIOCHEMISTRY

5.1 Electron transport of intra-erythrocytic P. berghei

P. berghei appears to depend for energy production on a form of electron transport which differs from that of the host[8]. It therefore provides a potential target for chemotherapeutic attack. Conventional inhibitors of electron transport and uncouplers not only inhibit chloroquine-induced pigment clumping[8] but also reduce the incorporation of adenosine into the parasites' nucleic acids (data given in the 3rd Quarterly Report 1976). The donor of electrons to the chain is not known.

Preliminary results have shown that treatment of the parasitized erythrocytes with menadione (10^{-4}M) or n-heptyl-4-hydroxyquinoline-N-oxide (10^{-5}M) reduced only slightly the utilization of glucose and the production of lactate by parasitized cells in vitro. This suggests that glucose metabolism may not be tightly linked to electron transport.

5.2 Cathepsins of parasitized erythrocytes

Our failure to isolate from P. berghei-parasitized cells a cathepsin D which was indisputably of parasite origin, and the presence of parasitized cells of a cathepsin D indistinguishable from that of mouse reticulocytes, prompted us to investigate the relationship between the number of parasites and the cathepsin activity of parasitized mouse red cells. Although results were somewhat variable (Table 54), there was little indication of an increase in catheptic activity as the parasitaemia rose. Instead, the apparent activity per parasitized cell fell, although the total activity for all cells remained approximately constant. This suggests that in the conditions used, little of the measured catheptic activity was due to the parasites. It is therefore probable that the parasites do not contain cathepsin D, and that other cathepsins must be present.

5.3 The effects of PABA on sporogonic development in P. berghei

As outlined in the 3rd Quarterly Report of 1976 (2.3.4) these studies were initiated to attempt to obtain results more statistically significant than those obtained by Ramkaran[9]. Initially, difficulties were encountered in the mosquito colony during our attempts to repeat this work. Abnormally high mortality rates and low infection rates in the mosquitoes were caused by excessive fluctuations of temperature and humidity in the insectaries. Examination of samples of the mosquito populations at the electron microscope level has not revealed the presence of concomitant, viral or microbial infections which might contribute to the vagaries in the malarial infections.

In recent experiments acceptable infection rates have been obtained in the mosquitoes but variations in the oocyst numbers within experimental batches are so great as to preclude the obtention of statistically significant results.

6. CONCLUSIONS AND RECOMMENDATIONS

The additional information gathered from our rodent causal prophylaxis studies has confirmed our belief that this is a valid model for tissue schizontocidal action. Taking into account the differences between our technique and that of Dr. L. H. Schmidt, there is a remarkably good parallel in our joint findings. The use of parenteral route in our rodent model will, we believe, permit us to detect activity in certain chemical groups (e.g. menoctone) the activity of which would be missed in the simian model.

During the coming year we will extend these observations and consolidate our data using both oral and parenteral routes of drug administration.

Extension of our long-term studies on drug combinations has provided useful leads for the possible protection of such promising new compounds as mefloquine. This work will be continued.

The mode of action of the antimalarials is still being investigated and fundamental gaps in our knowledge of parasite biochemistry are being exposed by our exploration of the drugs. Further work on these matters with special reference to mefloquine will be carried out during the coming year.

Studies will also be extended on the development of slow-release preparations of selected drugs.

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9 APPENDICES

Tables 1 through 14	The causal prophylactic potential of new Walter Reed compounds in rodent malaria model. Included are results of 110 Walter Reed 8-amino-quinolines plus 5 from other sources, 6-naphthyridines and 18 miscellaneous compounds. These data include an interpretation of minimum fully curative dosage (MFCD) presented in Schmidt's Final Report 1976.
Tables 15 through 38	The results of preliminary screening of compounds in causal prophylactic activity in the rodent screen.
Tables 39 through 53	Summary of data from causal prophylactic test in P. y. nigeriensis
Table 54	The relationship between parasitaemia and catheptic activity in P. berghei-infected mouse erythrocytes
Figure 1	A comparison of the rate of acquisition of resistance to mefloquine by the chloroquine-sensitive P. berghei N strain and the NS line which has a low level of resistance to chloroquine.
Figure 2	The acquisition of resistance to mefloquine by P. berghei NS line passaged under drug pressure (mefloquine 60 mg/kg sc at time of each passage), and its reversion to sensitivity on the release of drug selection pressure.
Figure 3	Rate of acquisition by P. berghei N strain of resistance to mefloquine, pyrimethamine and sulphaphenazole when the drugs are used alone.
Figure 4	Influence of combining mefloquine with pyrimethamine on the rate of acquisition of resistance to each drug by P. berghei in consecutive passages.
Figure 5	Influence of combining mefloquine with sulphaphenazole on the rate of acquisition of resistance to each drug by P. berghei N strain in consecutive passages.
Figure 6	Influence of combining mefloquine with primaquine on the rate of acquisition of resistance to each drug by P. berghei in consecutive passages.
Figure 7	Blood schizontocidal action of drug mixtures against P. berghei N strain in the "4-day test".

GROUP

8-aminoquinolines I Primaquine derivatives (a) variations in 1, 2, 3, 4 positions

LIV. No.	WR No.	BN No.	μM base/mg	s.c. M.F.E.D.	s.c. P.I.	p.o. M.F.E.D.	p.o. P.I.	Comments (toxicity, preliminary d
1370	2975E19	AG66475	2.2	66-132	1.0	66-132	1.0	Primaquine
1269		BG60018		Inactive at MTD	-			
1272	5990AC	AG99266	2.1	Inactive at MTD				MTD sc 63
1377		AG99266		Inactive at MTD		63-126	1.1	
1289	182234AA	BE10198	2.9	8.7-39	3.3			
1326	182234AD	BE17580	2.8	28-84	1.8			
1322	211814AB	BE12905	2.9	0.9-2.9	52.1			
1379				2.9-8.7	26.0	<8.7*	>11.4	
1273	181023AE	BD57427	2.1	63-210	0.7			
1373	181023AG	BE50003	2.1	63-210	0.7	21-63*	2.4	
1291	210550AA	BE11597	2.4	72-240	0.6			
1402	228002AA	BG58189	1.9	<5.7	>17.4	>MTD	-	MTD po 171
1387	219874AA	BE79802	2.5	2.5-7.5	19.8			
1451		ZN42821		>250*	<0.4			
1452	215733AA	ZN43328	2.5	Inactive at 250	-	Inactive at MTD	-	MTD po 75
1302	208442AA	ED57981	2.2	66-132	1.0			
1404	228335AA	BG60689	2.0	20-60	2.5	<60*	>1.7	
1268	183489AD	BD56671	2.5	Inactive at 1875	-			
1280	183489AE	BD57552	2.5	1875-2500	0.05			
1323	214703AA	BE15040	2.0	200-600	0.25			

MFED = minimum fully effective dose (daily) MFCD = minimum fully curative dose (daily mg/kg po) PI = prim

2

TABLE 1

I. Primaquine derivatives (a) variations in 1, 2, 3, 4 positions

ase/mg	s.c.		p.o.		Comments	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.	(toxicity, preliminary data, etc.)	M.F.C.D.	P.I.
2.2	66-132	1.0	66-132	1.0	Primaquine	1.1	1.0
	Inactive at MTD	-					
2.1	Inactive at MTD				MTD sc 63	1.05-2.1	0.5-1.04
	Inactive at MTD		63-126	1.1			
2.9	8.7-39	3.3				7.3-14.5	0.08-0.15
2.8	28-84	1.8					
2.9	0.9-2.9	52.1				9.7	0.11
	2.9-8.7	26.0	<8.7*	>11.4			
2.1	63-210	0.7				0.5-1.1	1.1-2.1
2.1	63-210	0.7	21-63*	2.4			
2.4	72-240	0.6				2.4	0.45
1.9	<5.7	>17.4	>MTD	-	MTD po 171	na	
2.5	2.5-7.5	19.8				1.25	0.9
	>250*	<0.4					
2.5	Inactive at 250	-	Inactive at MTD	-	MTD po 75	0.63-1.25	0.9-1.7
2.2	66-132	1.0				1.6-3.2	0.3-0.7
2.0	20-60	2.5	<60*	>1.7		na	
2.5	Inactive at 1875	-				2.5-5.0	0.2-0.4
2.5	1875-2500	0.05					
2.0	200-600	0.25				2Ø	

ctive dose MFCD = minimum fully curative dose (daily mg/kg po) PI = primaquine index

1

GROUP

I (a) continued

LIV. No.	WR No.	BN No.	μM base/mg	s.c. M.F.E.D.	s.c. P.I.	p.o. M.F.E.D.	p.o. P.I.	Comments (toxicity, preliminary da
1361	216893AA	BE19477	1.9	>570	<0.2			
1472	229427AA	BG70550	2.0	Inactive at 200*	-	>200	<0.5	
1355	219382AA	BE71226	2.1	63-126	1.0			
1356	219783AA	BE75948	1.7	Inactive at 1020	-			
1357	219784AA	BE75939	1.8	108-180	0.7			
1259	199507AB	BD24062	1.9	> MTD	-			MTD sc 57
1411	225374AA	BG37591	2.2	>MTD	-	<66*	>1.5	MTD sc 6.6
1305	211532AA	BE12567	1.9	>570	<0.2			Residual activity
1448		ZN41048		Inactive at 190	-	Inactive at 190	-	
1307	182232AC	BE08456	2.5	>750	<0.1			
1382	216100AA	BE17491	1.7	>170	<0.6			Residual activity
1470	224097AA	ZN43953	2.0	>200*	<0.5	>200*	<0.5	
1345	215295AA	BE16378	1.6	Inactive at 480				
1381				Inactive at 480				
1438	225448	BG37402	1.9	<57*	>1.7	<57*	>1.7	
1384	218676AA	BE55820	2.4	24-72	2.1			
1400	228000AA	BG58367	2.2	>MTD	-	<69*	>1.4	MTD sc 66
1138	106147AD	AY97897	2.2	22-66	2.3			
1432				66-220*	0.7	<66*	>1.5	
1383	217124AA	BE43759	1.8	54-108	1.2			

MFED = minimum fully effective dose (daily)

MFCD = minimum fully curative dose (daily mg/kg po)

PI = pri

TABLE 2 2

e/mg	s.c.		p.o.		Comments	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.	(toxicity, preliminary data, etc.)	M.F.C.D.	P.I.
9	>570	<0.2				19Ø	-
0	Inactive at 200*	-	>200	<0.5		na	
1	63-126	1.0		-		na	
7	Inactive at 1020	-				na	
8	108-180	0.7				na	
9	> MTD	-			MTD sc 57	19Ø	
2	>MTD	-	<66*	>1.5	MTD sc 6.6	na	
9	>570	<0.2			Residual activity	0.48-0.95	1.2-2.3
	Inactive at 190	-	Inactive at 190	-			
5	>750	<0.1				1.9-2.5	0.4-0.6
7	>170	<0.6			Residual activity	0.43-0.85	1.3-2.6
0	>200*	<0.5	>200*	<0.5		0.5-1.0	1.1-2.2
6	Inactive at 480					0.4-0.8	1.4-2.8
	Inactive at 480						
9	<57*	>1.7	<57*	>1.7		0.23-0.48	2.3-4.8
4	24-72	2.1				2.4Ø 24tox	
2	>MTD	-	<69*	>1.4	MTD sc 66	na	
2	22-66	2.3				3.3	0.3
	66-220*	0.7	<66*	>1.5			
8	54-108	1.2				0.9	1.2

tive dose MFCD = minimum fully curative dose (daily mg/kg po) PI = primaquine index

GROUP

I (a) continued

LIV. No.	WR No.	BN No.	μM base/mg	s.c. M.F.E.D.	s.c. P.I.	p.o. M.F.E.D.	p.o. P.I.	Comments (toxicity, preliminary d
1386	217154AA	BE67204	2.0	60-120	1.1			
1267	205439AA	BD54195	1.8	1.8-5.4	27.5			
1435				54-180*	1.0	5.4-18*	8.5	
1053	F 142		2.2	Inactive at MTD				MTD sc 220
1316				Inactive at MTD				
1056	157835	AW23379	2.2	1320-2200	0.06			Residual activity
1417	228708AA	BG66798	2.1	<21*	>4.7	<63 *	>1.6	
1446	228708AB	BG70756	2.1	<63*	>1.6	>63	<1.6	LD_{100} po <210
1414	228583AA	BG63664	2.3	>23	<4.3			LD_{66} sc/po ~ 69; LD_{10}
1445	228583AB	BG70729	2.3			<69	>1.4	LD_{100} sc <69; LD_{100}
1407	219130AA	BE58643	2.0	<60 *	>1.7	60-200 *	2.2	
1476	230388AA	BG81580	2.4	Inactive at 240	-	<72 *	>1.4	LD_{100} po <240
1454	216804AA	ZN43426	2.0	<60 *	>1.7			LD_{100} po <60

MFED = minimum fully effective dose (daily)

MFCD = minimum fully curative dose (daily mg/kg po)

PI = prim

TABLE 3

base/mg	s.c.		p.o.		Comments	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.	(toxicity, preliminary data, etc.)	M.F.C.D.	P.I.
2.0	60-120	1.1				1-2	0.6-1.1
1.8	1.8-5.4	27.5				1.8	0.6
	54-180*	1.0	5.4-18*	8.5			
2.2	Inactive at MTD				MTD sc 220	na	
	Inactive at MTD						
2.2	1320-2200	0.06			Residual activity	na	
2.1	<21*	>4.7	<63 *	>1.6			
2.1	<63*	>1.6	>63	<1.6	LD_{100} po <210		
2.3	>23	<4.3			LD_{66} sc/po ~ 69; LD_{100} sc/po <230		
2.3			<69	>1.4	LD_{100} sc <69; LD_{100} po <230		
2.0	<60 *	>1.7	60-200 *	2.2		na	
2.4	Inactive at 240	-	<72 *	>1.4	LD_{100} po <240	na	
2.0	<60 *	>1.7			LD_{100} po <60	0.25-1.0	1.1-4.4

ctive dose MFCD = minimum fully curative dose (daily mg/kg po) PI = primaquine index

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GROUP

8-aminoquinolines | Primaquine derivatives. (b) variations on terminal amino of side chai

LIV. No.	WR No.	BN No.	μM base/mg	s.c.		p.o.		Comments (toxicity, preliminary da
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1197	189294AB	BE46719	2.7	81-270	0.6			
1202	188303AA	BB45543	1.8	Inactive at 1800	-			
1082	161085AB	AX26820	1.0	Inactive at 30	-			
1378				30-60	2.2			
1282	182230AB	BD58040	2.5	>2500	<0.04			
1257	181721AB	BD27161	1.9	Inactive at 1900	-			
1304	181517AB	BE12370	2.3	69-230	0.7			
1058	F156		2.4	72-240	0.6			

MFED = minimum fully effective dose (daily)

MFCD = minimum fully curative dose (daily mg/kg po)

PI = prim

TABLE 4

es I Primaquine derivatives. (b) variations on terminal amino of side chains and other positions

base/mg	s.c.		p.o.		Comments	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.	(toxicity, preliminary data, etc.)	M.F.C.D.	P.I.
2.7	81-270	0.6				na	
1.8	Inactive at 1800	-				na	
1.0	Inactive at 30	-				2.5	0.4
	30-60	2.2					
2.5	> 2500	< 0.04				na	
1.9	Inactive at 1900	-				na	
2.3	69-230	0.7				na	
2.4	72-240	0.6				na	

ective dose MFCD = minimum fully curative dose (daily mg/kg po) PI = primaquine index

GROUP

8-aminoquinolines — I Primaquine derivatives — (c) variations on $-NH-\underset{\underset{C_2H_5}{|}}{CH}(CH_2)_3NH_2$

IV. No.	WR No.	BN No.	μM base/mg	s.c.		p.o.		Comments (toxicity, preliminary da
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1392	215761AA	BE16967	1.9	19-57	2.6	<57*	>1.7	
1393	226426AA	BG45208	2.7	2.7-8.1	18.3			LD_{100} sc/po 8?
1391	226296AA	BG44452	2.4	2.4-7.2	20.6	<72*	>1.4	
1409	226762AA	BG47293	2.5	>150*	<0.7	Inactive at 250*	-	

MFED = minimum fully effective dose (daily)

MFCD = minimum fully curative dose (daily mg/kg po)

PI = prim

2

TABLE 5

l Primaquine derivatives (c) variations on $-NH-\underset{\underset{C_2H_5}{|}}{CH}(CH_2)_3NH_2$

se/mg	s.c.		p.o.		Comments	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.	(toxicity, preliminary data, etc.)	M.F.C.D.	P.I.
1.9	19-57	2.6	<57*	>1.7		0.24	4.6
2.7	2.7-8.1	18.3			LD_{100} sc/po 81	na	
2.4	2.4-7.2	20.6	<72*	>1.4		na	
2.5	>150*	<0.7	Inactive at 250*	-		na	

ctive dose MFCD = minimum fully curative dose (daily mg/kg po) PI = primaquine index

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GROUP

8-aminoquinolines II Based on isopentaquine

LIV. No.	WR No.	BN No.	μM base/mg	s.c.		p.o.		Comments (toxicity, preliminary
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1375	6020AC	BE 21066	2.0			≈ 200	≈0.5	MTD po 200
1374	6020AD	BE20783	2.0			> MTD	-	MTD po 156
1371	6027AO	AG75828	3.7			111-222	0.6	
1303	210815AA	BE08527	1.9	> 57	<1.7			Residual activity
1290	210551AA	BE11588	2.2	> MTD	-			MTD sc 220

MFED = minimum fully effective dose (daily)

MFCD = minimum fully curative dose (daily mg/kg po)

PI = pri

TABLE 6

[1] Based on isopentaquine

se/mg	s.c.		p.o.		Comments	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.	(toxicity, preliminary data, etc.)	M.F.C.D.	P.I.
2.0			~ 200	~0.5	MTD po 200	na	
2.6			> MTD	-	MTD po 156		
3.7			111-222	0.6		3.7Ø	
1.9	> 57	<1.7			Residual activity	19	0.06
2.2	> MTD	-			MTD sc 220	22	0.05

ctive dose MFCD = minimum fully curative dose (daily mg/kg po) PI = primaquine index

GROUP

8 aminoquinolines III Based on quinocide

LIV. No.	WR No.	BN No.	μM base/mg	s.c.		p.o.		Comments (toxicity, preliminary c
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1385	152149AB	BE66770	2.8	> MTD	-			MTD sc 280
1325	215296AA	BE16369	2.1	6.3-21	7.3			
1388	222671AA	BG11891	2.1	63-126	1.0			
1413	228456AA	BG62807	2.4	< 7.2*	> 13.8			LD_{100} sc/po < 72
1439	221527AB	BG48898	2.5	< 7.5*	> 13.2			LD_{100} sc 25; po 75
1408	226937AA	BG55008	2.5	75-150*	0.9	75-250*	0.6	LD_{66} po ~ 250
1412	228457AA	BG62790	2.5	> 75 *	< 1.3	75-250*	0.6	LD_{100} sc < 250
1389	222890AA	BG13831	1.8	Inactive at 540	-			
1421	229238AA	BG70112	2.0	Inactive at 200*	-	> 200*	< 0.5	
1348	218335AA	BE66930	2.1	21-63	2.4			
1437				21-63	2.4	< 63 *	> 1.6	

MFED = minimum fully effective dose (daily)

MFCD = minimum fully curative dose (daily mg/kg po)

PI = pri

2

TABLE 7

III Based on quinocide

base/mg	s.c.		p.o.		Comments	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.	(toxicity, preliminary data, etc.)	M.F.C.D.	P.I.
2.8	> MTD	-			MTD sc 280	2.8	0.4
2.1	6.3-21	7.3				0.26	4.2
2.1	63-126	1.0				0.53-1.1	.05-2.1
2.4	< 7.2*	> 13.8			LD_{100} sc/po < 72		
2.5	< 7.5*	> 13.2			LD_{100} sc 25; po 75	0.3-1.25	0.9-3.5
2.5	75-150*	0.9	75-250*	0.6	LD_{66} po ~ 250	na	
2.5	> 75 *	< 1.3	75-250*	0.6	LD_{100} sc < 250		
1.8	Inactive at 540	-				0.9-1.8	0.6-1.2
2.0	Inactive at 200*	-	> 200*	< 0.5		na	
2.1	21-63	2.4				1.05-2.1	0.5-1.04
	21-63	2.4	< 63 *	> 1.6			

fective dose MFCD = minimum fully curative dose (daily mg/kg po) PI = primaquine index

1

GROUP

8-aminoquinolines IV Based on pentaquine

IV. No.	WR No.	BN No.	μM base/mg	s.c. M.F.E.D.	s.c. P.I.	p.o. M.F.E.D.	p.o. P.I.	Comments (toxicity, preliminary dat
1376	6021AK	BE20907	2.5			>250	<0.4	
1372	127854AC	BE20087	2.6			78-156	0.9	
1343	211674AB	BE20587	2.2	Inactive at 660	-			
1256	49577AE	BD27698	1.8	> MTD	-			MTD sc 54
1354	194343AA	BC06452	1.9	114-190	0.7			
1226	196469AA	BC51797	1.6	> 160	<0.6			Residual activity
1360	218670AB	BE59088	1.9	> MTD	-			MTD sc 190
1284	203608AA	BD27661	1.4	1.4-4.2	35.4			
1449		ZN42125		> 140*	<0.7	42-140*	1.1	
1283	203607AA	BD27652	1.4	42-140	1.1			
1434				42-140*	1.1	<42*	>2.4	
1255	202437AA	BD26164	1.6	16-48	3.1			
1433				<51 *	>1.9	<51*	>1.9	

MFED = minimum fully effective dose (daily)

MFCD = minimum fully curative dose (daily mg/kg po)

PI = prima

TABLE 8

IV Based on pentaquine

ase/mg	s.c.		p.o.		Comments	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.	(toxicity, preliminary data, etc.)	M.F.C.D.	P.I.
2.5			>250	<0.4		na	
2.6			78-156	0.9		1.3-2.6	0.4-0.9
2.2	Inactive at 660	-				na	
1.8	>MTD	-			MTD sc 54	18Ø	
1.9	114-190	0.7				19	0.06
1.6	>160	<0.6			Residual activity	na	
1.9	>MTD	-			MTD sc 190	na	
1.4	1.4-4.2	35.4				14	0.08
	>140*	<0.7	42-140*	1.1			
1.4	42-140	1.1				14	0.08
	42-140*	1.1	<42*	>2.4			
1.6	16-48	3.1				5.3-16	0.1-0.2
	<51*	>1.9	<51*	>1.9			

ctive dose MFCD = minimum fully curative dose (daily mg/kg po) PI = primaquine index

GROUP

8-aminoquinolines V. Sidechain on 8 with 6 carbons before NH_2 (a)

LIV. No.	WR No.	BN No.	μM base/mg	s.c.		p.o.		Comments (toxicity, preliminary da
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1380	212624AA	BE13822	1.9	57-114	1.1			
1416	228710AA	BG66412	2.3	<23 *	>4.3			LD_{50} sc ∿ 23; LD_{100} <
1350	211208AA	BE20005						Not sent
1453	212223AA	ZN43391	2.4	72-240*	0.6	72-240*	0.6	
1428	212579AB	BG48969	2.1	63-210*	0.7			
1410	226899AB	BG52623	2.4					LD_{100} sc/po <72

MFED = minimum fully effective dose (daily)

MFCD = minimum fully curative dose (daily mg/kg po)

PI = prima

TABLE 9

V. Sidechain on 8 with 6 carbons before NH_2 (a)

base/mg	s.c.		p.o.		Comments	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.	(toxicity, preliminary data, etc.)	M.F.C.D.	P.I.
1.9	57-114	1.1				0.95-1.9	0.6-1.1
2.3	<23 *	>4.3			LD_{50} sc ∿ 23; LD_{100} <69	na	
					Not sent	na	
2.4	72-240*	0.6	72-240*	0.6		0.6-2.4	0.5-1.8
2.1	63-210*	0.7				0.26-0.52	2.1-4.2
2.4					LD_{100} sc/po <72	na	

fective dose MFCD = minimum fully curative dose (daily mg/kg po) PI = primaquine index

1

GROUP

8-aminoquinolines V Sidechain on 8 with 6 carbons before NH_2 (b)

LIV. No.	WR No.	BN No.	μM base/mg	s.c. M.F.E.D.	s.c. P.I.	p.o. M.F.E.D.	p.o. P.I.	Comments (toxicity, preliminary d
1180	6025AO	BE21431	2.7	Inactive at 810	-			
1181	6026AI	AG75499		Inactive at MTD	-			MTD sc 240
1425	6026AD	BG14463	2.4					Not tested
1431	6026AI	AG75499		72-240*	0.6	<72*	>1.4	
1427	211666AB	BG11417	2.4	<72 *	>1.4			
1398	227495AA	BG56738	2.3	69-230*	0.7	>MTD *		LD_{66} sc 230; MTD po
1429	226257AA	BG44425	2.0	<60 *	>3.3			
1403	228327AA	BG60698	1.9	114-190	0.7	57-190*	0.8	
1426	226292AA	BG44541	2.3					LD_{100} sc <89

MFED = minimum fully effective dose (daily)

MFCD = minimum fully curative dose (daily mg/kg po)

PI = pri

TABLE 10

V. Sidechain on 8 with 6 carbons before NH_2 (b)

base/mg	s.c. M.F.E.D.	s.c. P.I.	p.o. M.F.E.D.	p.o. P.I.	Comments (toxicity, preliminary data, etc.)	Schmidt data M.F.C.D.	Schmidt data P.I.
2.7	Inactive at 810	-				na	
	Inactive at MTD	-			MTD sc 240		
2.4					Not tested		
	72-240*	0.6	<72*	>1.4		1.2	0.9
2.4	<72 *	>1.4				2.4	0.45
2.3	69-230*	0.7	>MTD *		LD_{66} sc~230; MTD po 69	na	
2.0	<60 *	>3.3				na	
1.9	114-190	0.7	57-190*	0.8		na	
2.3					LD_{100} sc<69	na	

ctive dose MFCD = minimum fully curative dose (daily mg/kg po) PI = primaquine index

1

GROUP

8-aminoquinolines VI Piperazine linkages on position 8

LIV. No.	WR No.	BN No.	μM base/mg	s.c.		p.o.		Comments (toxicity, preliminary d
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1399	227681AA	BG56612	2.0	120-200	0.6			Activity principally resid
1154	BW349C59		1.7	17-51	2.9			
1362				17-51	2.9			
1442	229406AA	BG70603	1.9	Inactive at 114*	-	Inactive at 190*	-	
1477	230395AA	BG81599	1.8	Inactive at 180*	-	Inactive at 180*	-	
1478	230394AA	BG81606	1.9	Inactive at 190*	-	Inactive at 190*	-	
1440	229431AA	BG70578	2.0	>120 *	<0.8	Inactive at 200*	-	
1441	229397AA	BG70596	1.9	>114 *	<0.9	>190*	<0.5	
1443	229396AA	BG70630	1.9	>114 *	<0.9	Inactive at 190*		
1444	229398AA	BG70658	1.9	Inactive at 114*	-	Inactive at 190*	-	
1471	229429AA	BG70667	1.8	Inactive at 180*	-	Inactive at 180*	-	

MFED = minimum fully effective dose (daily)

MFCD = minimum fully curative dose (daily mg/kg po)

PI = prin

2

TABLE 11

VI Piperazine linkages on position 8

base/mg	s.c.		p.o.		Comments	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.	(toxicity, preliminary data, etc.)	M.F.C.D.	P.I.
2.0	120-200	0.6			Activity principally residual	na	
1.7	17-51	2.9				na	
	17-51	2.9					
1.9	Inactive at 114*	-	Inactive at 190*	-		na	
1.8	Inactive at 180*	-	Inactive at 180*	-		na	
1.9	Inactive at 190*	-	Inactive at 190*	-		na	
2.0	>120 *	<0.8	Inactive at 200*	-		na	
1.9	>114 *	<0.9	>190*	<0.5		na	
1.9	>114 *	<0.9	Inactive at 190*			na	
1.9	Inactive at 114*	-	Inactive at 190*	-		na	
1.8	Inactive at 180*	-	Inactive at 180*	-		na	

fective dose MFCD = minimum fully curative dose (daily mg/kg po) PI = primaquine index

/

GROUP

8-aminoquinolines VII Miscellaneous types

LIV. No.	WR No.	BN No.	μM base/mg	s.c. M.F.E.D.	s.c. P.I.	p.o. M.F.E.D.	p.o. P.I.	Comments (toxicity, preliminary da
1279	179443AC	BD57436	5.3	Inactive at 1590	-			
1270	189296AA	BB46595	3.0	Inactive at 900	-			
1271	189296AB	BC09186		Inactive at 900	-			
1262	206027AA	BD54471	3.1	> MTD	-			MTD sc 310
1473	4396AR	BG44621	2.1	Inactive at MTD*	-	Inactive at MTD*	-	MTD sc 60; po 30
1390	211533AC	BG38034	2.0	Inactive at 300	-	Inactive at 200	-	MTD sc 300
1436	211533AB	BE12601	2.0	Inactive at 200*	-	Inactive at 60*	-	LD_{100} po<200
1344	211816AA	BE20630	2.5	75-150	0.9			
1346	29594AC	BE20014	3.1	31-93	1.6			
1184	7312AI	BB47761	2.3	Inactive at 2300	-			
1264	29634AB	BD04622	1.9	57-190	0.8			
1401	227988AA	BG58447	2.0	Inactive at 600	-	60-200*	0.8	
1419	229011AA	BG67099	2.0	60-200*	0.8	> 200 *	<0.5	LD_{50} sc ∿200
1314	213640AA	BE09999	2.0	>600	<0.2			
1347	218336AA	BE66832	2.1	210-630	0.2			
1334	201678AB	BE13304	2.1	21-63	2.4			
1447		ZN40130		66-220*	0.7	<66 *	>1.5	
1420	229092AA	BG68354	2.9	Inactive at 290*	-	Inactive at 290*	-	
1482	230212AA	BG80994	2.2	Inactive at 220*	-	Inactive at 220*	-	
1043	Ni 147/36	Dann	2.7	8.1-27	5.6			
1044	Ba138/11		2.6	26-78	1.9			

MFED = minimum fully effective dose (daily)

MFCD = minimum fully curative dose (daily mg/kg po)

PI = prim

TABLE 12

2

VII Miscellaneous types

base/mg	s.c. M.F.E.D.	s.c. P.I.	p.o. M.F.E.D.	p.o. P.I.	Comments (toxicity, preliminary data, etc.)	Schmidt data M.F.C.D.	Schmidt data P.I.
5.3	Inactive at 1590	-				na	
3.0	Inactive at 900	-				na	
	Inactive at 900	-					
3.1	> MTD	-			MTD sc 310	3.1Ø	
2.1	Inactive at MTD*	-	Inactive at MTD*	-	MTD sc 60; po 30	na	
2.0	Inactive at 300	-	Inactive at 200	-	MTD sc 300	1.0	1.1
2.0	Inactive at 200*	-	Inactive at 60*	-	LD_{100} po < 200		
2.5	75-150	0.9				25	0.04
3.1	31-93	1.6				3.1	0.35
2.3	Inactive at 2300	-				23Ø	-
1.9	57-190	0.8				19Ø	-
2.0	Inactive at 600	-	60-200	0.8		na	
2.0	60-200*	0.8	> 200 *	< 0.5	LD_{50} sc ~200	na	
2.0	> 600	< 0.2				na	
2.1	210-630	0.2				na	
2.1	21-63	2.4				21Ø	
	66-220*	0.7	< 66 *	> 1.5		--	
2.9	Inactive at 290*	-	Inactive at 290*	-		na	
2.2	Inactive at 220*	-	Inactive at 220*	-		na	
2.7	8.1-27	5.6				na	
2.6	26-78	1.9				na	

fective dose MFCD = minimum fully curative dose (daily mg/kg po) PI = primaquine index

1

GROUP

Naphthyridines

LIV. No.	WR No.	BN No.	μM base/mg	s.c.		p.o.		Comments (toxicity, preliminary de
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1485	206287AB	BG81759	2.3	Inactive at 230*	-	Inactive at 230*	-	
1487	222119	BG81740	2.2	Inactive at 220*	-			
1278	206218AA	BD54766	1.5	>750	<0.1			Residual activity only
1287	210446AA	BE10983	1.6	Inactive at LD_{30}	-			LD_{30} sc ∿ 160
1286	210447AA	BE10965	3.3	Inactive at LD_{30}	-			LD_{30} sc ∿ 990
1288	210434AA	BE11024	4.3	Inactive at LD_{30}	-			LD_{30} sc ∿ 1280

MFED = minimum fully effective dose (daily)

MFCD = minimum fully curative dose (daily mg/kg po)

PI = prin

2

TABLE 13

base/mg	s.c.		p.o.		Comments	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.	(toxicity, preliminary data, etc.)	M.F.C.D.	P.I.
2.3	Inactive at 230*	-	Inactive at 230*	-		na	
2.2	Inactive at 220*	-				na	
1.5	>750	<0.1			Residual activity only	na	
1.6	Inactive at LD_{30}	-			LD_{30} sc $\sim$ 160	na	
3.3	Inactive at LD_{30}	-			LD_{30} sc $\sim$ 990	na	
4.3	Inactive at LD_{30}	-			LD_{30} sc $\sim$ 1280	na	

ective dose MFCD = minimum fully curative dose (daily mg/kg po) PI = primaquine index

GROUP

Miscellaneous compounds

LIV. No.	WR No.	BN No.	μM base/mg	s.c.		p.o.		Comments (toxicity, preliminary da
				M.F.E.D.	P.I.	M.F.E.D.	P.I.	
1484	230284AA	BG81222	2.3	Inactive at 230*	-	Inactive at 230*	-	
1483	230225AA	BG81035	2.1	Inactive at 210*	-	Inactive at 210*	-	LD_{33} po ∼ 210
1486	230621AA	BG83191	2.3	Inactive at 230*	-	> 230 *	< 0.4	LD_{33} po ∼ 230
1479	230387AA	BG81615	2.9	< 290	> 0.3	Inactive at 290*	-	
1480	230386AA	BG81624	2.2	Inactive at 220*	-	> 220 *	< 0.4	
1474	206513AB	BG79017	2.1	> 210 *	< 0.5	> 210 *	< 0.5	
1481	230216AA	BG80967	1.7	Inactive at 170*	-	Inactive at 170*	-	
1430	129577AC	AW41662	2.0	Inactive at 200*	-	Inactive at 200*	-	
1422	194965AD	BG43991	2.7	< 81 *	> 1.2	> 270 *	< 0.4	
1415	228769AA	BG66403	1.6	Inactive at 160*	-	Inactive at 160*	-	
1423	225449AA	BG37573	2.8	< 84 *	> 1.2	< 84 *	> 1.2	
1405	220594AA	BE84652	2.1	> 126 *	> 0.8	Inactive at 210*	-	
1406	220679AA	BE96303	2.3	< 138 *	> 0.7	Inactive at 230*	-	
1418	229046AA	BG67179	2.6	78-260*	0.6	Inactive at 260*	-	
1394	226626AA	BG46714	2.4	2.4-7.2	20.6	72-240*	0.6	
1395	199361AC	BG47168	3.0	3.0-9.0	16.5	< 90 *	> 1.1	
1203	182058	AY98947	3.2	3.2-9.6	15.5			Guanidine derivative
1251	190830	BD29165	2.2	66-220	0.7			Diamidine

MFED = minimum fully effective dose (daily)

MFCD = minimum fully curative dose (daily mg/kg po)

PI = prin

TABLE 14

ompounds

ase/mg	s.c.		p.o.		Comments	Schmidt data	
	M.F.E.D.	P.I.	M.F.E.D.	P.I.	(toxicity, preliminary data, etc.)	M.F.C.D.	P.I.
2.3	Inactive at 230*	-	Inactive at 230*	-		na	
2.1	Inactive at 210*	-	Inactive at 210*	-	LD_{33} po ~ 210	na	
2.3	Inactive at 230*	-	> 230 *	< 0.4	LD_{33} po ~ 230	na	
2.9	< 290	> 0.3	Inactive at 290*	-		na	
2.2	Inactive at 220*	-	> 220 *	< 0.4		na	
2.1	> 210 *	< 0.5	> 210 *	< 0.5		na	
1.7	Inactive at 170*	-	Inactive at 170*	-		na	
2.0	Inactive at 200*	-	Inactive at 200*	-		na	
2.7	< 81 *	> 1.2	> 270 *	< 0.4		na	
1.6	Inactive at 160*	-	Inactive at 160*	-		na	
2.8	< 84 *	> 1.2	< 84 *	> 1.2		na	
2.1	> 126 *	> 0.8	Inactive at 210*	-		na	
2.3	< 138 *	> 0.7	Inactive at 230*	-		na	
2.6	78-260*	0.6	Inactive at 260*	-		na	
2.4	2.4-7.2	20.6	72-240*	0.6		na	
3.0	3.0-9.0	16.5	< 90 *	> 1.1		na	
3.2	3.2-9.6	15.5			Guanidine derivative	32 Ø	
2.2	66-220	0.7			Diamidine	22 Ø	

ctive dose

MFCD = minimum fully curative dose (daily mg/kg po)

PI = primaquine index

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS

TABLE 15

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1370	2975	AG64745	po	1.0				✓	2.2	Primaquine
				10.0			✓		22.0	
				30.0		✓			66.0	
				60.0	✓				132.0	
				100.0	✓				220.0	
1371	6027	AG75828	po	1.0				✓	3.7	4-methyl isopentaquin
				10.0				✓	37.0	
				30.0		✓			111.0	
				60.0	✓				222.0	
				100.0	✓				370.0	
1372	127854	BE20087	po	1.0				✓	2.6	4-methyl pentaquine
				10.0				✓	26.0	
				30.0		✓			78.0	
				60.0	✓				156.0	
				100.0	✓				260.0	

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PRINCIPAL INVESTIGATOR: Professor W. Peters

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CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS TABLE 16

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1373	181023	BE50003	po	1.0				✓	2.1	4-methyl primaquine
				10.0			✓		21.0	
				30.0	✓				63.0	
				60.0	✓				126.0	
				100.0	✓				210.0	$\sim LD_{33}$
1374	6020AD	BE20783	po	1.0				✓	2.6	isopentaquine oxalate
				10.0			✓		26.0	
				30.0			✓		78.0	
				60.0		✓			156.0	
				100.0	✓				260.0	$\sim LD_{66}$
1375	6020AC	BE21066	po	30.0		✓			60.0	isopentaquine diphasphate
				60.0		✓			120.0	
				100.0	✓				200.0	
1376	6021	BE20907	po	1.0				✓	2.5	Pentaquine
				10.0			✓		25.0	
				30.0	✓				75.0	
				100.0	✓				250.0	$\sim LD_{33}$

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CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS

TABLE 17

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1377	5990	AG99266	sc	10.0				✓	221.0	
				30.0				✓	63.0	$\sim LD_{33}$
				100.0					210.0	$> LD_{100}$
1377	5990	AG99266	po	3.0				✓	6.3	
				30.0			✓		63.0	
				60.0	✓				126.0	
1378	161085	AX26820	sc	10.0				✓	10.0	
				30.0		✓			30.0	
				100.0	✓				100.0	$\sim LD_{33}$
1378	161085	AX26820	po	3.0			✓		3.0	
				30.0	✓				30.0	
1379	211814	BE12905	sc	1.0		✓			2.9	
				10.0	✓				29.0	
				30.0	✓				87.0	
				100.0					290.0	$> LD_{100}$
1379	211814	BE12905	po	3.0	✓				8.7	
				30.0	✓				87.0	

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PRELIMINARY SCREEN RESULTS TABLE 18

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1380	212624	BE13822	sc	10.0				✓	19.0	
				30.0			✓		57.0	
				100.0	✓				190.0	
1381	215295	BE16378	sc	10.0				✓	16.0	
				30.0				✓	48.0	
				100.0			✓		160.0	3/3 Patent but delayed
				300.0			✓		480.0	
1382	216100	BE17491	sc	1.0				✓	1.7	
				10.0				✓	17.0	
				30.0				✓	51.0	
				100.0	✓				170.0	
1383	217124	BE43759	sc	1.0				✓	1.8	
				10.0			✓		18.0	
				30.0	✓				54.0	
				100.0	✓				180.0	

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PRINCIPAL INVESTIGATOR: Professor W. Peters

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Date ..... DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS

TABLE 19

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1384	218676	BE55820	sc	1.0				✓	2.4	
				10.0	✓				24.0	
				30.0	✓				72.0	
				100.0					240.0	$>LD_{100}$
1385	152149	BE66770	sc	30.0			✓		84.0	
				100.0		✓			280.0	
				300.0					840.0	$>LD_{100}$
1386	217154	BE67204	sc	1.0				✓	2.0	
				10.0		✓			20.0	
				30.0	✓				60.0	
				100.0	✓				200.0	
1387	219874	BE79802	sc	1.0				✓	2.5	
				10.0	✓				25.0	
				30.0	✓				75.0	
				100.0					250.0	$>LD_{100}$
1388	222671	BG11891	sc	30.0			✓		63.0	
				60.0		✓			126.0	
				100.0	✓				210.0	

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CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS TABLE 20

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1389	222890	BG13831	sc	30.0			✓		54.0	
				100.0		✓			180.0	
1389	222890	BG13831	po	30.0				✓	54.0	
				100.0				✓	180.0	
1390	211533	BG38034	sc	30.0			✓		60.0	
				100.0			✓		200.0	
1390	211533	BG38034	po	30.0				✓	60.0	
				100.0				✓	200.0	
1391	226296	BG44452	sc	1.0			✓		2.4	
				10.0	✓				24.0	
				30.0	✓				72.0	$\sim LD_{66}$
				100.0					240.0	$> LD_{100}$
1391	226296	BG44452	po	30.0	✓				72.0	$\sim LD_{66}$
				100.0					240.0	$> LD_{100}$
1392	215761	BE16967	sc	1.0			✓		1.9	
				10.0	✓				19.0	
				30.0	✓				57.0	
				100.0	✓				190.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

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Date ..... DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS TABLE 21

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1392	215761	BE16967	po	30.0	✓				57.0	
				100.0	✓				190.0	
1393	226426	BG45208	sc	1.0	✓				2.7	
				10.0	✓				27.0	
				30.0					81.0	$>LD_{100}$
				100.0					270.0	$>LD_{100}$
1393	226426	BG45208	po	30.0					81.0	$>LD_{100}$
				100.0					270.0	$>LD_{100}$
1394	226626	BG46714	sc	1.0			✓		2.4	
				10.0	✓				24.0	
				30.0	✓				72.0	
				100.0	✓				240.0	
1394	226626	BG46714	po	30.0		✓			72.0	
				100.0	✓				240.0	
1395	199361	BG47168	sc	1.0			✓		3.0	
				10.0	✓				30.0	
				30.0	✓				90.0	
				100.0	✓				300.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

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Date ..... DEC 1978

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS TABLE 22

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1395	199361	BG47168	po	30.0	✓				90.0	
				100.0	✓				300.0	
1396	206891	BG47462	sc	1.0				✓	2.9	
				10.0				✓	29.0	
				30.0	✓				87.0	
				100.0	✓				290.0	
1396	206891	BG47462	po	30.0		✓			87.0	
				100.0	✓				290.0	
1397	216693	BG47239	sc	30.0				✓	111.0	
				100.0				✓	370.0	
1397	216693	BG47239	po	30.0	✓				111.0	
				100.0	✓				370.0	
1398	227495	BG56738	sc	30.0		✓			69.0	
				100.0	✓				230.0	$\sim LD_{66}$
1398	227495	BG56738	po	30.0		✓			69.0	$\sim LD_{33}$
				100.0					230.0	$> LD_{100}$

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

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Date ..... 4 DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS

TABLE 23

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1399	227681	BG56612	sc	30.0				✓	60.0	
				100.0	✓				200.0	
1399	227681	BG56612	po	30.0	✓				60.0	
				100.0	✓				200.0	
1400	228000	BG58367	sc	30.0			✓		69.0	
				100.0	✓				230.0	$\approx LD_{33}$
1400	228000	BG58367	po	30.0	✓				69.0	
				100.0					230.0	$> LD_{100}$
1401	227988	BG58447	sc	30.0				✓	60.0	
				100.0				✓	200.0	
1401	227988	BG58447	po	30.0		✓			60.0	
				100.0	✓				200.0	
1402	228002	BG58189	sc	30.0	✓				60.0	
				60.0	✓				120.0	
1402	228002	BG58189	po	30.0		✓			60.0	$\approx LD_{33}$
				100.0					200.0	$> LD_{100}$

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date ..... DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS TABLE 24

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1403	228327	BG60698	sc	30.0			✓		57.0	
				100.0	✓				190.0	
1403	228327	BG60698	po	30.0			✓		57.0	
				100.0	✓				190.0	
1404	228335	BG60689	sc	30.0	✓				63.0	
				100.0	✓				210.0	
1404	228335	BG60689	po	30.0	✓				63.0	
				100.0	✓				210.0	
1405	220594	BE84652	sc	30.0			✓		63.0	
				60.0		✓			126.0	
1405	220594	BE84652	po	30.0				✓	63.0	
				100.0				✓	210.0	
1406	220679	BE96303	sc	30.0	✓				69.0	
				60.0	✓				138.0	
1406	220679	BE96303	po	30.0				✓	69.0	
				100.0				✓	230.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date ..... DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS

TABLE 25

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1407	219130	BE58643	sc	30.0	✓				60.0	
				60.0	✓				120.0	
1407	219130	BE58643	po	30.0		✓			60.0	
				100.0	✓				200.0	
1408	226937	BG55008	sc	30.0			✓		75.0	
				60.0	✓				150.0	
1408	226937	BG55008	po	30.0			✓		77.5	
				100.0	✓				250.0	$\sim LD_{66}$
1409	226762	BG47293	sc	30.0		✓			75.0	
				60.0		✓			150.0	
1409	226762	BG47293	po	30.0				✓	75.0	
				100.0				✓	250.0	
1410	226899	BG52623	sc	30.0					72.0	$> LD_{100}$
				60.0					144.0	$> LD_{100}$
1410	226899	BG52623	po	30.0					72.0	$> LD_{100}$
				100.0					240.0	$> LD_{100}$

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date ..... 21st DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS TABLE 26

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1411	225374	BG37591	sc	30.0	✓				66.0	
				100.0					220.0	$>LD_{100}$
1411	225374	BG37591	po	30.0	✓				66.0	
				100.0	✓				220.0	
1412	228457	BG62790	sc	10.0		✓			25.0	
				30.0		✓			75.0	
				100.0					250.0	$>LD_{100}$
1412	228457	BG62790	po	30.0		✓			75.0	
				100.0	✓				250.0	
1413	228456	BG62807	sc	3.0	✓				7.2	
				10.0	✓				24.0	
				30.0					72.0	$>LD_{100}$
				100.0					240.0	$>LD_{100}$
1413	228456	BG62807	po	30.0					72.0	$>LD_{100}$
				100.0					240.0	$>LD_{100}$

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date ..... DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS TABLE 27

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1414	228583	BG63644	sc	3.0		✓			6.9	
				10.0		✓			23.0	
				30.0	✓				69.0	$\sim LD_{66}$
				100.0					230.0	$> LD_{100}$
1414	228583	BG63644	po	30.0	✓				69.0	$\sim LD_{66}$
				100.0					230.0	$> LD_{100}$
1415	228769	BG66403	sc	10.0				✓	16.0	
				30.0				✓	48.0	
				100.0				✓	160.0	
1415	228769	BG66403	po	30.0				✓	48.0	
				100.0				✓	160.0	
1416	228710	BG66412	sc	10.0	✓				23.0	$\sim LD_{50}$
				30.0					69.0	$> LD_{100}$
				100.0					230.0	$> LD_{100}$
1416	228710	BG66412	po	30.0					69.0	$> LD_{100}$
				100.0					230.0	$> LD_{100}$

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date ..... DEC 1979

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS

TABLE 28

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1417	228708	BG66798	sc	10.0	✓				21.0	
				30.0	✓				63.0	
				100.0	✓				210.0	$\sim LD_{66}$
1417	228708	BG66798	po	30.0	✓				63.0	
				100.0					210.0	$> LD_{100}$
1418	229046	BG67179	sc	30.0		✓			78.0	
				100.0	✓				260.0	
1418	229046	BG67179	po	30.0				✓	78.0	
				100.0				✓	260.0	
1419	229011	BG67099	sc	30.0		✓			60.0	
				100.0	✓				200.0	$\sim LD_{50}$
1419	229011	BG67099	po	30.0				✓	60.0	
				100.0			✓		200.0	
1420	229092	BG68354	sc	30.0				✓	87.0	
				100.0				✓	290.0	
1420	229092	BG68354	po	30.0				✓	87.0	
				100.0				✓	290.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date ..... DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS TABLE 29

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1421	229238	BG70112	sc	30.0				✓	60.0	
				100.0				✓	200.0	
1421	229238	BG70112	po	30.0				✓	60.0	
				100.0			✓		200.0	
1422	194965	BG33940	sc	30.0	✓				81.0	
				60.0	✓				162.0	
1422	194965	BG33940	po	30.0				✓	81.0	
				100.0		✓			270.0	
1423	225449	ZN43971	sc	30.0	✓				84.0	
				100.0	✓				280.0	
1423	225449	ZN43971	po	30.0	✓				84.0	
				100.0	✓				280.0	
1426	226292	BG44541	sc	30.0					69.0	$> LD_{100}$
				100.0					230.0	$> LD_{100}$
1427	211666	BG11417	sc	30.0	✓				72.0	
				100.0	✓				240.0	
1428	212579	BG48969	sc	30.0				✓	63.0	
				100.0	✓				210.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date ..... 1 DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS TABLE 30

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1429	226257	BG44425	sc	30.0	✓				60.0	
				100.0	✓				200.0	
1430	129577	AW41662	sc	30.0				✓	60.0	
				100.0				✓	200.0	
1430	129577	AW41662	po	30.0				✓	60.0	
				100.0				✓	200.0	
1431	6026	AG75499	sc	30.0				✓	72.0	
				100.0	✓				240.0	~ LD_{66}
1431	6026	AG75499	po	30.0	✓				72.0	
				100.0	✓				240.0	
1432	106147	AY97897	sc	30.0				✓	66.0	
				100.0	✓				220.0	
1432	106147	AY97897	po	30.0	✓				66.0	
				100.0	✓				220.0	~ LD_{33}
1433	202437	BD26164	sc	30.0	✓				51.0	
				100.0	✓				170.0	
1433	202437	BD26164	po	30.0	✓				51.0	
				100.0	✓				170.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date ..... 7 DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS

TABLE 31

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1434	203607	BD27652	sc	30.0				✓	42.0	
				100.0	✓				140.0	
1434	203607	BD27652	po	30.0	✓				42.0	
				100.0	✓				140.0	
1435	205439	BD54195	sc	30.0				✓	54.0	
				100.0	✓				180.0	
1435	205439	BD54195	po	3.0			✓		5.4	
				10.0	✓				18.0	
				30.0	✓				54.0	
1436	211533	BE12601	sc	30.0				✓	60.0	
				100.0				✓	200.0	
1436	211533	BE12601	po	30.0			✓		60.0	
				100.0					200.0	$>LD_{100}$
1437	218335	BE66930	po	30.0	✓				63.0	
				100.0	✓				210.0	$\sim LD_{50}$

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

DEC 1976

Date .....

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS TABLE 32

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	uM Base/Kg	Comment
1438	225448	BG37402	sc	30.0	✓				57.0	$\sim LD_{66}$
				100.0					190.0	$> LD_{100}$
1438	225448	BG37402	po	30.0	✓				57.0	
				100.0	✓				190.0	$\sim LD_{66}$
1439	221527	BG48898	sc	3.0	✓				7.5	
				10.0					25.0	$> LD_{100}$
				30.0					75.0	$> LD_{100}$
				100.0					250.0	$> LD_{100}$
1439	221527	BG48898	po	30.0					75.0	$> LD_{100}$
				100.0					250.0	$> LD_{100}$
1440	229431	BG70578	sc	30.0				✓	60.0	
				60.0			✓		120.0	
1440	229431	BG70578	po	30.0				✓	60.0	
				100.0				✓	200.0	
1441	229397	BG70596	sc	30.0			✓		57.0	
				60.0			✓		114.0	
1441	229397	BG70596	po	30.0				✓	57.0	
				100.0			✓		190.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date 5 DEC 1976 .....

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS

TABLE 33

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1442	229406	BG70603	sc	30.0				✓	57.0	
				60.0				✓	114.0	
1442	229406	BG70603	po	30.0				✓	57.0	
				100.0				✓	190.0	
1443	229396	BG70630	sc	30.0				✓	57.0	
				60.0			✓		114.0	
1443	229396	BG70630	po	30.0				✓	57.0	
				100.0				✓	190.0	
1444	229398	BG70658	sc	30.0				✓	57.0	
				60.0				✓	114.0	
1444	229398	BG70658	po	30.0				✓	57.0	
				100.0				✓	190.0	
1445	228583	BG70729	sc	30.0					69.0	$> LD_{100}$
				60.0					138.0	$> LD_{100}$
1445	228583	BG70729	po	30.0	✓				69.0	
				100.0					230.0	$> LD_{100}$

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date 15 DEC 1976 .....

PRELIMINARY SCREEN RESULTS TABLE 34

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1446	228708	BG70756	sc	30.0	✓				63.0	
				60.0	✓				126.0	
1446	228708	BG70756	po	30.0		✓			63.0	
				100.0					210.0	$>LD_{100}$
1447	201678	ZN40130	sc	30.0			✓		66.0	
				100.0	✓				220.0	
1447	201678	ZN40130	po	30.0	✓				66.0	
				100.0	✓				220.0	
1448	211532	ZN41048	sc	30.0				✓	57.0	
				100.0				✓	190.0	
1448	211532	ZN41048	po	30.0				✓	57.0	
				100.0				✓	190.0	
1449	203608	ZN42125	sc	30.0				✓	42.0	
				100.0		✓			140.0	
1449	203608	ZN42125	po	30.0		✓			42.0	
				100.0	✓				140.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date 7 DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS TABLE 35

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	uM Base/Kg	Comment
1450	215296	ZN42812	sc	30.0	✓				66.0	
				100.0	✓				220.0	
1450	215296	ZN42812	po	30.0	✓				66.0	
				100.0	✓				220.0	
1451	219874	ZN42821	sc	30.0				✓	75.0	
				100.0		✓			250.0	
1451	219874	ZN42821	po	30.0					75.0	$> LD_{100}$
				100.0					250.0	$> LD_{100}$
1452	215733	ZN43328	sc	30.0				✓	75.0	
				100.0			✓		250.0	$\sim LD_{33}$
1452	215733	ZN43328	po	30.0				✓	75.0	
				100.0					250.0	$> LD_{100}$
1453	212223	ZN43391	sc	30.0				✓	72.0	
				100.0	✓				240.0	
1453	212223	ZN43391	po	30.0		✓			72.0	
				100.0	✓				240.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date ..... 6th DEC 19

PRELIMINARY SCREEN RESULTS TABLE 36

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1454	216804	ZN43426	sc	30.0	✓				60.0	
				100.0	✓				200.0	
1454	216804	ZN43426	po	30.0					60.0	$> LD_{100}$
				100.0					200.0	$> LD_{100}$
1455	215761	ZN44030	sc	30.0	✓				60.0	
				100.0	✓				200.0	
1455	215761	ZN44030	po	30.0	✓				60.0	
				100.0	✓				200.0	
1470	224097	ZN43953	sc	30.0				✓	60.0	
				100.0			✓		200.0	
1470	224097	ZN43953	po	30.0				✓	60.0	
				100.0		✓			200.0	
1471	229429	BG70667	sc	30.0				✓	54.0	
				100.0				✓	180.0	
1471	229429	BG70667	po	30.0				✓	54.0	
				100.0				✓	180.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date ..... DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS TABLE 37

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1472	229427	BG70550	sc	30.0				✓	60.0	
				100.0				✓	200.0	
1472	229427	BG70550	po	30.0			✓		60.0	
				100.0		✓			200.0	
1473	4396	BG66421	sc	30.0				✓	63.0	
				100.0				✓	210.0	$\sim LD_{66}$
1473	4396	BG66421	po	30.0				✓	63.0	
				100.0					210.0	$> LD_{100}$
1474	206513	BG79017	sc	30.0			✓		63.0	
				100.0			✓		210.0	
1474	206513	BG79017	po	30.0			✓		63.0	
				100.0		✓			210.0	
1476	230388	BG81580	po	30.0	✓				72.0	
				100.0					240.0	$> LD_{100}$
1477	230395	BG81599	po	30.0				✓	54.0	
				100.0				✓	180.0	
1478	230394	BG81606	po	30.0				✓	54.0	
				100.0				✓	180.0	

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date 7 DEC 1976

CAUSAL PROPHYLAXIS

PRELIMINARY SCREEN RESULTS TABLE 38

Category 1 = ? Fully active = 0/3 Patent
2 = ? Active = 1/3 Patent
3 = ? Slightly active = 2/3 Patent
4 = Inactive = 3/3 Patent

LIV	WR	BN	Route	Dose mg/kg x 1	1	2	3	4	μM Base/Kg	Comment
1479	230387	BG81615	po	30.0				✓	87.0	
				100.0				✓	290.0	
1480	230386	BG81624	po	30.0				✓	66.0	
				100.0			✓		220.0	
1481	230216	BG80967	po	30.0				✓	51.0	
				100.0				✓	170.0	
1482	230212	BG80994	po	30.0				✓	66.0	
				100.0				✓	220.0	
1483	230225	BG81035	po	30.0				✓	63.0	
				100.0				✓	210.0	$\sim LD_{33}$
1484	230284	BG81222	po	30.0				✓	69.0	
				100.0				✓	230.0	
1485	206287	BG81759	po	30.0				✓	69.0	
				100.0				✓	230.0	
1486	230621	BG83191	po	30.0				✓	69.0	
				100.0			✓		230.0	$\sim LD_{33}$

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

PRINCIPAL INVESTIGATOR: Professor W. Peters

Signed .....

Date .....8 DEC 1976.....

CAUSAL PROPHYLAXIS TEST NO.: BR 531 DATE: 26.11.76

DRUG: LIV/1411 WR 225374 BOTTLE NO. BC

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME AF

VERTEBRATE HOST: ♂TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylac activity
∅	5/5	3/3	3/3	5.93	3.72	3.71			
3.0	2/3		3/3	>8.59		3.68	$>2.66-\left[\frac{1.72\times1.68}{1.71}-1.72\right]$	-0.03	>2.69
10.0	3/3*		0/3**	5.72		-	-0.21		
30.0	0/3**		0/3**	-		-			

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY: Nil at 3.0 mg/kg PRINCIPAL INVE

* 1/3 died ** 3/3 died

2

ST NO.: BR 531 DATE: 26.11.76 TABLE 39

LIV/1411 WR 225374 BOTTLE NO. BG37591

H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2 hrs.

mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylactic activity	
5.93	3.72	3.71				
>8.59		3.68	$>2.66-\left[\frac{1.72 \times 1.68}{1.71}-1.72\right]$	-0.03	>2.69	Slightly active
5.72		-	-0.21			$\sim LD_{66}$
-		-				$>LD_{100}$

DOSE.....mg/kg

Nil at 3.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

* 1/3 died ** 3/3 died

CAUSAL PROPHYLAXIS TEST NO.: BR531 DATE: 26.11.76

DRUG: LIV/1404 WR 228335 BOTTLE NO. BG

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME A

VERTEBRATE HOST: ♂TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP [illegible] P			(a = 2) ACTIVITY VALUES		
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophyla activity
ø	5/5	3/3	3/3	5.93	3.72	3.71			
3.0	2/3		3/3	>8.51		3.71	$>2.58-\left[\frac{1.72\times1.71}{1.71}-1.72\right]$	0	>2.58
10.0	2/3		3/3	>8.86		4.28	$>2.93-\left[\frac{1.72\times2.28}{1.71}-1.72\right]$	0.57	>2.36
30.0	0/3		3/3	>14		3.74	$>8.07-\left[\frac{1.72\times1.74}{1.71}-1.72\right]$	0.03	>8.04

MINIMUM FULLY ACTIVE DOSE.....10.0-30.0.....mg/kg

RESIDUAL ACTIVITY: Nil at 30.0 mg/kg PRINCIPAL INVE

2

TEST NO.: BR531 DATE: 26.11.76 TABLE 40

LIV/1404 WR 228335 BOTTLE NO. BG 60689

80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/po TIME AFTER INFECTION: 2 hrs.

TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

	GMP 2% P			(a = 2) ACTIVITY VALUES			
x	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylactic activity	COMMENT
	5.93	3.72	3.71				
	>8.51		3.71	$>2.58-\left[\frac{1.72\times1.71}{1.71}-1.72\right]$	0	>2.58	Slightly active
	>8.86		4.28	$>2.93-\left[\frac{1.72\times2.28}{1.71}-1.72\right]$	0.57	>2.36	Slightly active
	>14		3.74	$>8.07-\left[\frac{1.72\times1.74}{1.71}-1.72\right]$	0.03	>8.04	Fully active

VE DOSE.....10.0-30.0.....mg/kg

Nil at 30.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 531 DATE: 26.11.76

DRUG: LIV/1403 WR 228327 BOTTLE NO. BG

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME A

VERTEBRATE HOST: ♂TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylac activity
~~Ø~~	5/5	3/3	3/3	5.93	3.72	3.71			
60.0	1/3		3/3	>11.27		3.77	$>5.34-\left[\frac{1.72 \times 1.77}{1.71}-1.72\right]$	0.06	>5.2
100.0	0/3		3/3	>14		3.74	$>8.07-\left[\frac{1.72 \times 1.74}{1.71}-1.72\right]$	0.03	>8.0

MINIMUM FULLY ACTIVE DOSE.....60-100.....mg/kg

RESIDUAL ACTIVITY: Nil at 100.0 mg/kg PRINCIPAL INVES

2

NO.: BR 531 DATE: 26.11.76 TABLE 41

LIV/1403 WR 228327 BOTTLE NO. BG60698

H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2 hrs.

mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylactic activity	
5.93	3.72	3.71				
>11.27		3.77	$>5.34-\left[\frac{1.72 \times 1.77}{1.71}-1.72\right]$	0.06	>5.28	Active
>14		3.74	$>8.07-\left[\frac{1.72 \times 1.74}{1.71}-1.72\right]$	0.03	>8.04	Fully active

DOSE.....60-100.....mg/kg

Nil at 100.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 563 DATE: 17.1.77

DRUG: LIV/1402 WR 228002 BOTTLE NO. B

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME A

VERTEBRATE HOST: ♂TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	$C^o/_To$	XC	$C^x/_Tx$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophyla activity
Ø	5/5	3/3	3/3	5.35	4.95	3.63			
3.0	0/3		3/3	>14.00		4.05	$>8.65-\left[\frac{2.95\times 2.05}{1.63}-2.95\right]$	0.76	> 7.
10.0	0/3		3/3	>14.00		3.91	$>8.65-\left[\frac{2.95\times 1.91}{1.63}-2.95\right]$	0.51	> 8.
30.0	0/3*		0/3**	>14.00		-			

MINIMUM FULLY ACTIVE DOSE.....≤3.0.....mg/kg

RESIDUAL ACTIVITY: Nil at 10.0 mg/kg PRINCIPAL INVE

* 2/3 died 1** 3/3 died

2

NO.: BR 563 DATE: 17.1.77 TABLE 42

LIV/1402 WR 228002 BOTTLE NO. BG 58189

H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2 hrs.

mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylactic activity	
5.35	4.95	3.63				
>14.00		4.05	$> 8.65-\left[\frac{2.95 \times 2.05}{1.63}-2.95\right]$	0.76	> 7.89	Fully active
>14.00		3.91	$> 8.65-\left[\frac{2.95 \times 1.91}{1.63}-2.95\right]$	0.51	> 8.14	Fully active
>14.00		-				$\sim LD_{80}$

OSE.....<3.0.....mg/kg

at 10.0 mg/kg

/3 died 1** 3/3 died

PRINCIPAL INVESTIGATOR: Professor W. Peters

1

CAUSAL PROPHYLAXIS TEST NO.: BR 563 DATE: 17.1.77

DRUG: LIV/1401 WR 227988 BOTTLE NO. BG 58

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFT

VERTEBRATE HOST: ♂TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylacti activity
∅	5/5	3/3	3/3	5.35	4.95	3.63			
100.0	3/3		3/3	5.11		3.40	$-0.24-\left[\frac{2.95 \times 1.40}{1.63}-2.95\right]$	-0.41	0.17
300.0	3/3		3/3	5.35		3.72	$0-\left[\frac{2.95 \times 1.72}{1.63}-2.95\right]$	0.16	-0.16

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY: Nil at 300.0 mg/kg PRINCIPAL INVEST

2

NO.: BR 563 DATE: 17.1.77 TABLE 43

LIV/1401 WR 227988 BOTTLE NO. BG 58447

H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 hrs.

mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylactic activity	
5.35	4.95	3.63				
5.11		3.40	$-0.24-\left[\frac{2.95\times1.40}{1.63}-2.95\right]$	-0.41	0.17	Inactive
5.35		3.72	$0-\left[\frac{2.95\times1.72}{1.63}-2.95\right]$	0.16	-0.16	Inactive

OSE.....mg/kg

Nil at 300.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 563 DATE: 17.1.77

DRUG: LIV/ 1400 WR 228000 BOTTLE NO.

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME

VERTEBRATE HOST: ♂TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophyl activi
∅	5/5	3/3	3/3	5.35	4.95	3.63			
60.0	0/3*		1/3**	-		4.18			

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY: PRINCIPAL INV

*3/3 died ** 2/3 died

2

ST NO.: BR 563 DATE: 17.1.77 TABLE44

LIV/ 1400 WR 228000 BOTTLE NO. BG58367

H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2 hrs.

W mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylactic activity	
5.35	4.95	3.63				
-		4.18				$\sim LD_{80}$

DOSE.....mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

ed ** 2/3 died

CAUSAL PROPHYLAXIS TEST NO.: BR564 DATE: 20.1.77

DRUG: LIV/1399 WR 227681 BOTTLE NO.

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME

VERTEBRATE HOST: ♂TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophy activit
Ø	5/5	3/3	2/2	5.30	3.67	4.05			
60.0	1/3		3/3	>11.17		3.85	$>5.87-\left[\frac{1.67\times1.85}{2.05}-1.67\right]$	-0.16	>6.
100.0	0/3		0/3	>14.00		>14.00	$>8.70-\left[\frac{1.67\times12.00}{2.05}-1.67\right]$	8.11	>0.

MINIMUM FULLY ACTIVE DOSE.....60-100.....mg/kg

RESIDUAL ACTIVITY: Very marked at 100 mg/kg PRINCIPAL INVES

2

NO.: BR564 DATE: 20.1.77 TABLE 45

LIV/1399 WR 227681 BOTTLE NO. BG 56612

20 ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 hrs.

mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylactic activity	
5.30	3.67	4.05				
11.17		3.85	$>5.87-\left[\frac{1.67\times1.85}{2.05}-1.67\right]$	-0.16	>6.03	Active
14.00		>14.00	$>8.70-\left[\frac{1.67\times12.00}{2.05}-1.67\right]$	8.11	>0.59	Prophylactic activity masked by strong residual activity

OSE 60-100 .....mg/kg

marked at 100 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 564 DATE: 20.1.77

DRUG: LIV/1395 WR 199361 BOTTLE NO. B

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME A

VERTEBRATE HOST: ♂TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophyla activity
∅	5/5	3/3	2/2	5.30	3.67	4.05			
1.0	3/3		3/3	6.35		3.95	$1.05-\left[\frac{1.67\times1.95}{2.05}-1.67\right]$	-0.08	1.
3.0	0/6		3/3	>14.00		4.78	$>8.70-\left[\frac{1.67\times2.78}{2.05}-1.67\right]$	0.59	>8.
10.0	0/3		3/3	>14.00		5.61	$>8.70-\left[\frac{1.67\times3.61}{2.05}-1.67\right]$	1.27	>7.

MINIMUM FULLY ACTIVE DOSE.....1.0-3.0.....mg/kg

RESIDUAL ACTIVITY: Nil at 3.0 mg/kg
Slight at 10.0 mg/kg

PRINCIPAL INVE

2

EST NO.: BR 564 DATE: 20.1.77 TABLE 46

LIV/1395 WR 199361 BOTTLE NO. BG 47168

O/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 hrs.

FW mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

	GMP 2% P			(a = 2) ACTIVITY VALUES			
x	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylactic activity	COMMENT
2	5.30	3.67	4.05				
3	6.35		3.95	$1.05-\left[\frac{1.67\times1.95}{2.05}-1.67\right]$	-0.08	1.13	Inactive
3	>14.00		4.78	$>8.70-\left[\frac{1.67\times2.78}{2.05}-1.67\right]$	0.59	>8.11	Fully active
3	>14.00		5.61	$>8.70-\left[\frac{1.67\times3.61}{2.05}-1.67\right]$	1.27	>7.43	Fully active

VE DOSE.....1.0-3.0.....mg/kg

Nil at 3.0 mg/kg
Slight at 10.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 536 DATE: 6.12.76

DRUG: LIV/1394 WR 226626 BOTTLE NO. BG4

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME AF

VERTEBRATE HOST: ♂TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylac activity
∅	5/5	3/3	3/3	5.10	5.02	3.59			
1.0	2/3		3/3	>8.10		3.53	$>3.00-\left[\frac{3.02\times1.53}{1.59}-3.02\right]$	-0.11	>3.11
3.0	0/3		3/3	>14		3.45	$>8.90-\left[\frac{3.02\times1.45}{1.59}-3.02\right]$	-0.27	>9.17
10.0	0/3		2/2	>14		3.68	$>8.90-\left[\frac{3.02\times1.68}{1.59}-3.02\right]$	0.17	>8.73

MINIMUM FULLY ACTIVE DOSE.....1.0-3.0.....mg/kg

RESIDUAL ACTIVITY: Nil at 10.0 mg/kg PRINCIPAL INVEST

2

T NO.: BR 536 DATE: 6.12.76 TABLE 47

LIV/1394 WR 226626 BOTTLE NO. BG46714

/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 hrs.

V mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylactic activity	
5.10	5.02	3.59				
>8.10		3.53	$>3.00-\left[\frac{3.02\times1.53}{1.59}-3.02\right]$	-0.11	> .11	Slightly active
>14		3.45	$>8.90-\left[\frac{3.02\times1.45}{1.59}-3.02\right]$	-0.27	>9.17	Fully active
>14		3.68	$>8.90-\left[\frac{3.02\times1.68}{1.59}-3.02\right]$	0.17	>8.	Fully active

DOSE.....1.0-3.0.....mg/kg

Nil at 10.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 532 DATE: 30.11.76

DRUG: LIV/ 1393 WR 226426 BOTTLE NO. B

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME

VERTEBRATE HOST: ♂TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophyla activity
Ø	5/5	3/3	3/3	5.26	3.67	3.66			
0.3	2/3		3/3	> 8.71		4.01	$>3.45-\left[\frac{1.67\times 2.01}{1.66}-1.67\right]$	0.35	> 3.
1.0	1/3		3/3	>11.60		4.15	$>6.34-\left[\frac{1.67\times 2.15}{1.66}-1.67\right]$	0.49	>5.8
3.0	0/3		3/3	>14		3.92	$>8.74-\left[\frac{1.67\times 1.92}{1.66}-1.67\right]$	0.26	>8.4

MINIMUM FULLY ACTIVE DOSE.....1.0 - 3.0 m.....mg/kg

RESIDUAL ACTIVITY: Nil at 3.0 mg/kg PRINCIPAL INVE

2

EST NO.: BR 532 DATE: 30.11.76 TABLE 48

LIV/ 1393 WR 226426 BOTTLE NO. BG 45208

30/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 hrs.

FW mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

	GMP 2% P			(a = 2) ACTIVITY VALUES			
x	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylactic activity	COMMENT
3	5.26	3.67	3.66				
3	> 8.71		4.01	$> 3.45-\left[\frac{1.67 \times 2.01}{1.66}-1.67\right]$	0.35	> 3.10	Slightly active
3	>11.60		4.15	$>6.34-\left[\frac{1.67 \times 2.15}{1.66}-1.67\right]$	0.49	>5.85	Active
3	>14		3.92	$>8.74-\left[\frac{1.67 \times 1.92}{1.66}-1.67\right]$	0.26	>8.48	Fully active

E DOSE.....1.0 - 3.0 m.....mg/kg

il at 3.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 536 DATE: 6.12.76

DRUG: LIV/ 1392 WR 215761 BOTTLE NO. BE 1

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME A

VERTEBRATE HOST: ♂TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylac activity
∅	5/5	3/3	3/3	5.10	5.02	3.59			
30.0	0/3		3/3	>14		3.52	$>8.90-\left[\frac{3.02 \times 1.52}{1.59}-3.02\right]$	-0.13	>9.2

MINIMUM FULLY ACTIVE DOSE.....≤30.....mg/kg

RESIDUAL ACTIVITY: Nil at 30.0 mg/kg PRINCIPAL INVES

2

T NO.: BR 536 DATE: 6.12.76 TABLE 49

LIV/ 1392 WR 215761 BOTTLE NO. BE 16967

H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 hrs.

mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylactic activity	
5.10	5.02	3.59				
>14		3.52	$>8.90-\left[\frac{3.02 \times 1.52}{1.59}-3.02\right]$	-0.13	>9.20	Fully active

OSE.....<30.....mg/kg

Nil at 30.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 536 DATE: 6.12.76

DRUG: LIV/1391 WR 226296 BOTTLE NO. B

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME

VERTEBRATE HOST: ♂ TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophy activi
Ø	5/5	3/3	3/3	5.10	5.02	3.59			
0.3	3/3		3/3	5.01		3.83	$-0.09-\left[\frac{3.02 \times 1.83}{1.59}-3.02\right]$	0.46	-0
1.0	2/3		3/3	> 8.47		4.51	$>3.37-\left[\frac{3.02 \times 2.51}{1.59}-3.02\right]$	1.75	>1

MINIMUM FULLY ACTIVE DOSE.....>1.0.....mg/kg

RESIDUAL ACTIVITY: Slight at 1.0 mg/kg PRINCIPAL INV

2

T NO.: BR 536 DATE: 6.12.76 TABLE 50

LIV/1391 WR 226296 BOTTLE NO. BG44452

/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 hrs.

W mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
$f/_h$	b	$c/_e$	$(h - f) - \left[\frac{(b-a)(e-a)}{(c-a)} - (b-a)\right]$	Residual activity	Prophylactic activity	
5.10	5.02	3.59				
5.01		3.83	$-0.09 - \left[\frac{3.02 \times 1.83}{1.59} - 3.02\right]$	0.46	-0.55	Inactive
>8.47		4.51	$>3.37 - \left[\frac{3.02 \times 2.51}{1.59} - 3.02\right]$	1.75	>1.62	Slightly active

E DOSE.....>1.0.....mg/kg

light at 1.0 mg/kg PRINCIPAL INVESTIGATOR: Professor W. Peters

CAUSAL PROPHYLAXIS TEST NO.: BR 536 DATE: 6.12.76

DRUG: LIV/ 1390 WR 211533 BOTTLE NO. BG

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME A

VERTEBRATE HOST: ♂TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophyl activit
∅	5/5	3/3	3/3	5.10	5.02	3.59			
100.0	3/3		3/3	5.39		3.75	$0.29-\left[\frac{3.02 \times 1.75}{1.59}-3.02\right]$	0.30	-0.
150.0	3/3		2/3*	5.90		3.54	$0.80-\left[\frac{3.02 \times 1.54}{1.59}-3.02\right]$	-0.10	0.

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY: Nil at 150.0 mg/kg PRINCIPAL INVE

* 1/3 died

2

EST NO.: BR 536 DATE: 6.12.76 TABLE 51

LIV/ 1390 WR 211533 BOTTLE NO. BG 38034

O/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2 hrs.

FW mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

	GMP 2% P			(a = 2) ACTIVITY VALUES			
x	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylactic activity	COMMENT
/3	5.10	5.02	3.59				
/3	5.39		3.75	$0.29-\left[\frac{3.02 \times 1.75}{1.59}-3.02\right]$	0.30	-0.01	Inactive
/3*	5.90		3.54	$0.80-\left[\frac{3.02 \times 1.54}{1.59}-3.02\right]$	-0.10	0.90	Inactive

VE DOSE.....mg/kg

Nil at 150.0 mg/kg

* 1/3 died

PRINCIPAL INVESTIGATOR: Professor W. Peters

1

CAUSAL PROPHYLAXIS TEST NO.: BR532 DATE: 30.11.76

DRUG: LIV/1387 WR 219874 BOTTLE NO. BE

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME A

VERTEBRATE HOST: ♂ TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophyla activity
Ø	5/5	3/3	3/3	5.26	3.67	3.66			
1.0	1/3		3/3	>11.30		4.33	$>6.04-\left[\frac{1.67\times 2.33}{1.66}-1.67\right]$	0.67	> 5.
3.0	0/3		3/3	>14		4.66	$>8.74-\left[\frac{1.67\times 2.66}{1.66}-1.67\right]$	1.01	> 7.

MINIMUM FULLY ACTIVE DOSE.....1.0 - 3.0.....mg/kg

RESIDUAL ACTIVITY: Slight at 3.0 mg/kg PRINCIPAL INVE

2

T NO.: BR532 DATE: 30.11.76 TABLE 52

LIV/1387 WR 219874 BOTTLE NO. BE 79802

H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2 hrs.

V mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylactic activity	
5.26	3.67	3.66				
>11.30		4.33	$>6.04-\left[\frac{1.67 \times 2.33}{1.66}-1.67\right]$	0.67	> 5.37	Active
>14		4.66	$>8.74-\left[\frac{1.67 \times 2.66}{1.66}-1.67\right]$	1.01	> 7.73	Fully active

E DOSE.....1.0 - 3.0.....mg/kg

Slight at 3.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

1

CAUSAL PROPHYLAXIS TEST NO.: BR532 DATE:30.11.76

DRUG: LIV/1386 WR 217154 BOTTLE NO. BE

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME

VERTEBRATE HOST: ♂TFW mice PARASITE (SUB) SPECIES: P. y. nigeriensis

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES		
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophyl activit
∅	5/5	3/3	3/3	5.26	3.67	3.66			
30.0	2/3		3/3	> 8.66		3.60	$> 3.40-\left[\frac{1.67 \times 1.60}{1.66}-1.67\right]$	-0.06	> 3.
60.0	1/3		3/3	>11.46		3.55	$> 6.20-\left[\frac{1.67 \times 1.55}{1.66}-1.67\right]$	-0.11	> 6.

MINIMUM FULLY ACTIVE DOSE.....>60.0.....mg/kg

RESIDUAL ACTIVITY: Nil at 60.0 mg/kg PRINCIPAL INVE

2

ST NO.: BR532 DATE: 30.11.76 TABLE 53

LIV/1386 WR 217154 BOTTLE NO. BE 67204

H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 hrs.

W mice PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
$f/_h$	b	$c/_e$	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual activity	Prophylactic activity	
5.26	3.67	3.66				
>8.66		3.60	$>3.40-\left[\frac{1.67\times1.60}{1.66}-1.67\right]$	-0.06	>3.34	Slightly active
>11.46		3.55	$>6.20-\left[\frac{1.67\times1.55}{1.66}-1.67\right]$	-0.11	>6.09	Active

E DOSE.....>60.0.....mg/kg

Nil at 60.0 mg/kg

PRINCIPAL INVESTIGATOR: Professor W. Peters

TABLE 54

The relationship between parasitaemia and catheptic activity in *P. berghei*-infected mouse erythrocytes

Experiment	Day	Parasitaemia (%)	Catheptic activity per cell*	
			All cells	Parasitized cells
I	4	10	1.98	19.8
	5	18	1.22	6.8
	6	29	1.73	5.9
	7	39	1.43	3.7
II	3	5	2.55	51.0
	5	14	2.85	20.4
	6	30	4.43	14.54
	.	38	2.61	6.77
	10	42	6.13	2.62

* arbitrary units

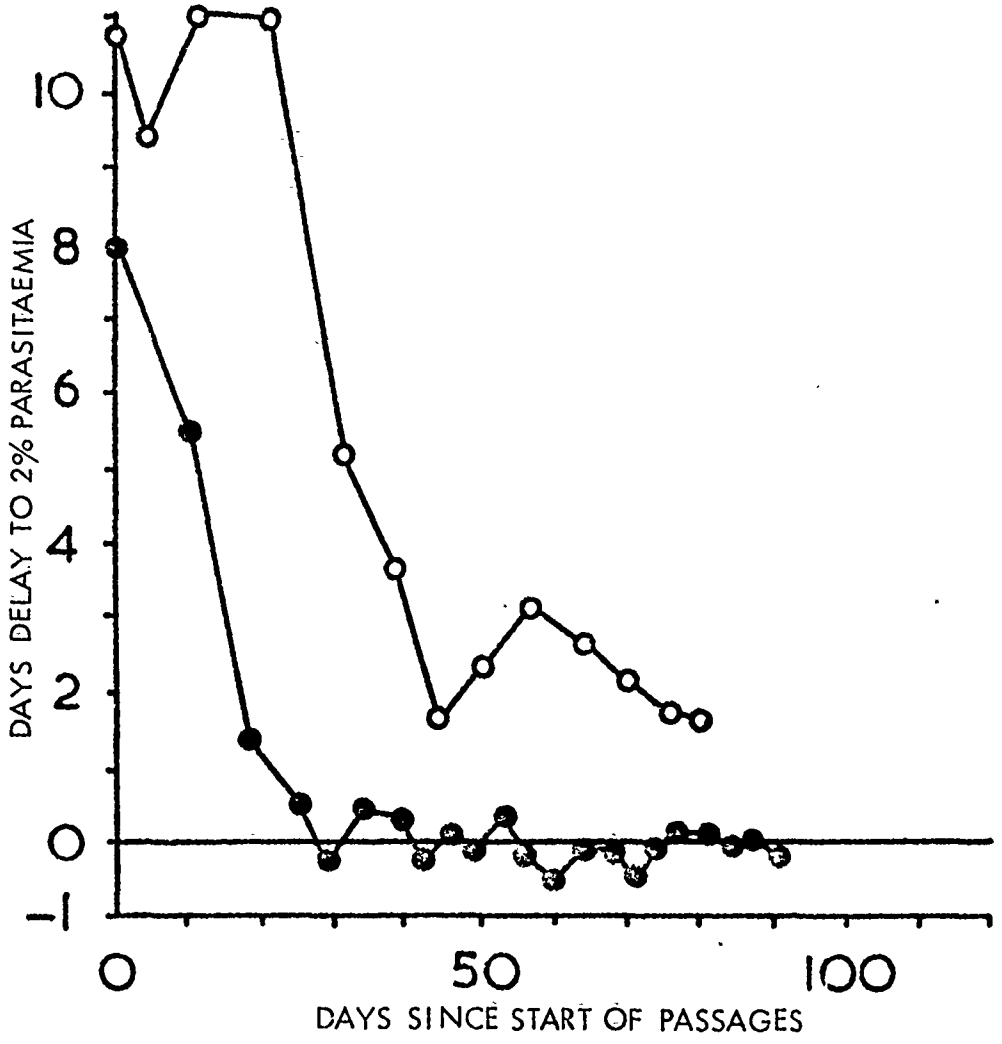

FIGURE 1

A comparison of the rate of acquisition of resistance to mefloquine by the chloroquine-sensitive P. berghei N strain and the NS line which has a low level of resistance to chloroquine.

o—o N strain exposed to a single dose of 30 mg/kg mefloquine on the day of passage.

●—● NS line exposed to 60 mg/kg mefloquine sc on the day of passage.

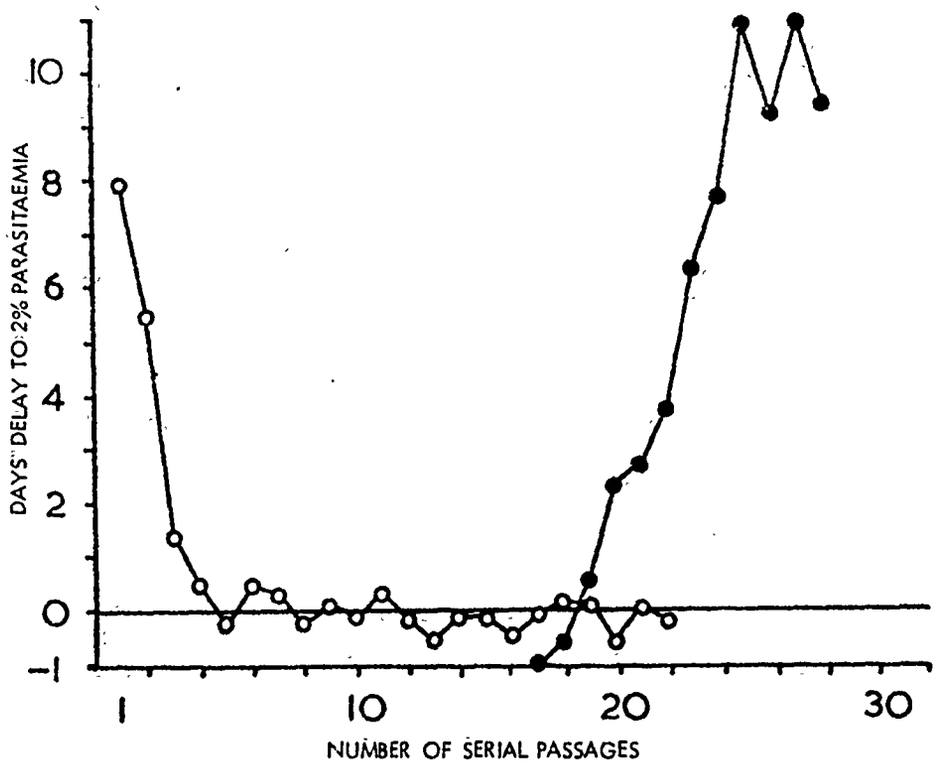

FIGURE 2

The acquisition of resistance to mefloquine by P. berghei NS line passaged under drug pressure (mefloquine 60 mg/kg sc at time of each passage), and its reversion to sensitivity on the release of drug selection pressure.

o—o passages under drug pressure.
•—o passages without selection pressure.

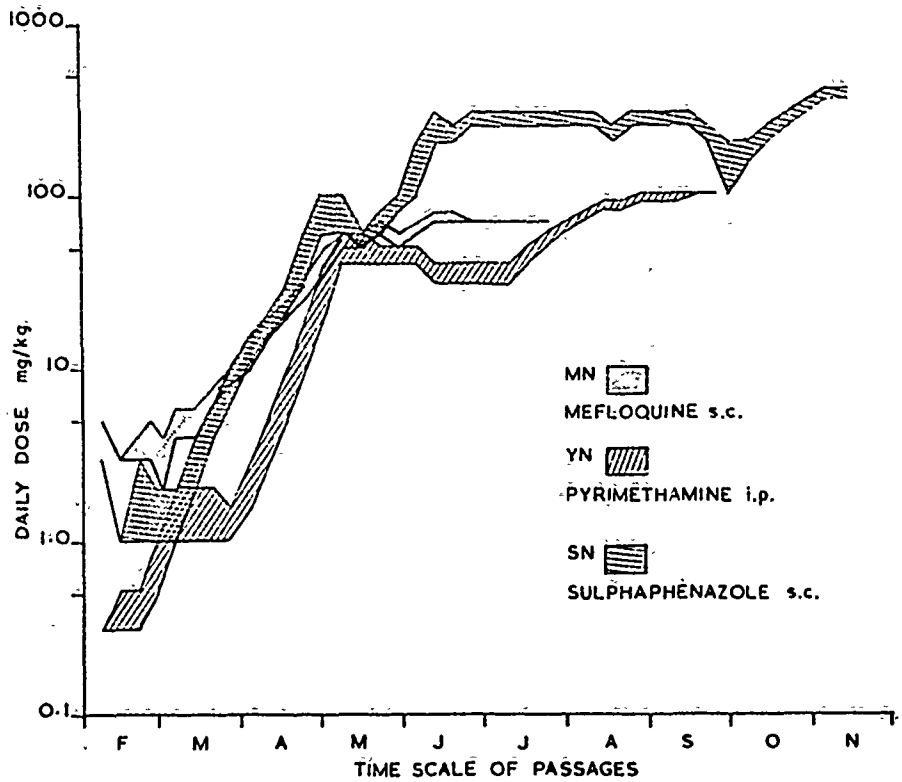

FIGURE 3.

Rate of acquisition by P. berghei N strain of resistance to mefloquine, pyrimethamine and sulphaphenazole when the drugs are used alone. Consecutive passages were exposed to increasing drug doses, given daily for 6 days of each week, the passages being made on the 7th day.

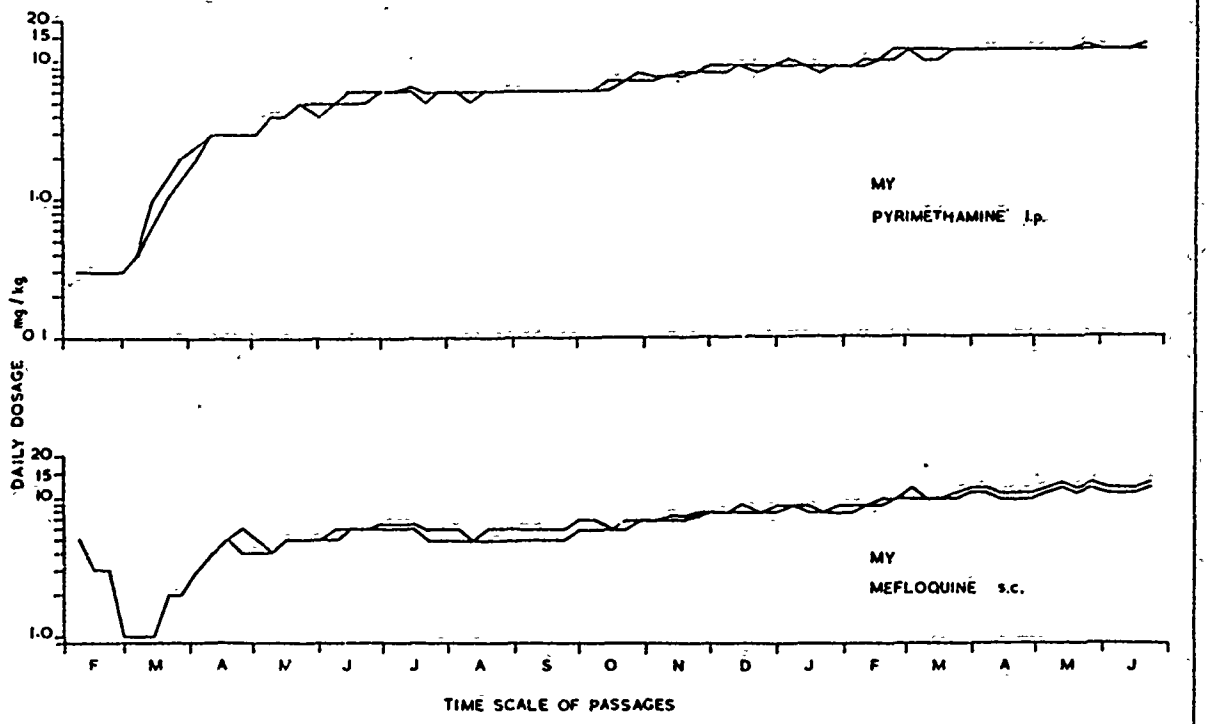

FIGURE 4

Influence of combining mefloquine with pyrimethamine on the rate of acquisition of resistance to each drug by P. berghei in consecutive passages. Top lines indicate maximum levels of pyrimethamine and lower lines of mefloquine in the mixture at each passage (cf Figure 3).

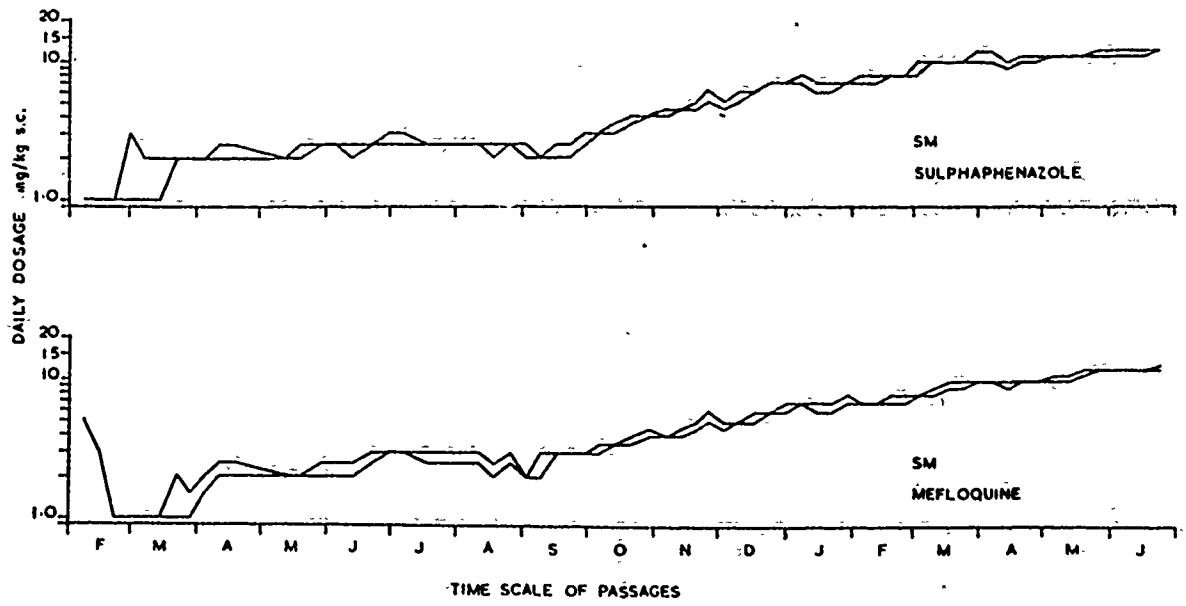

FIGURE 5

Influence of combining mefloquine with sulphaphenazole on the rate of acquisition of resistance to each drug by P. berghei N strain in consecutive passages. Top lines indicate maximum levels of sulphaphenazole and bottom lines of mefloquine in the mixtures at each passage (cf Figure 3).

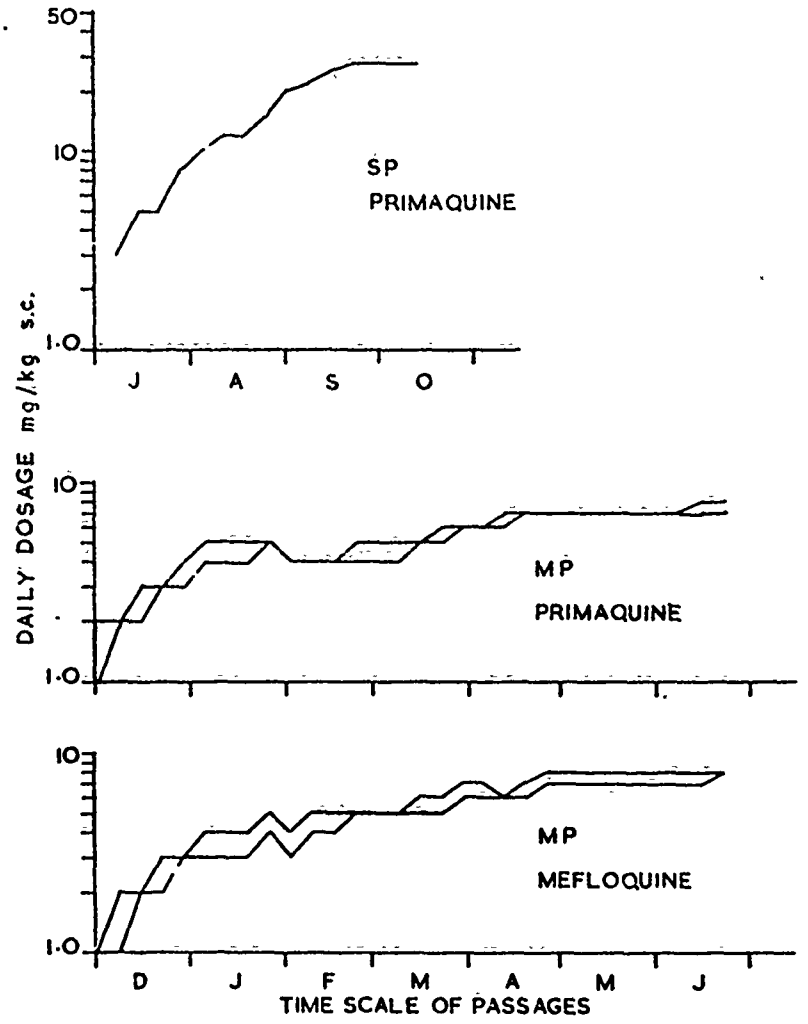

FIGURE 6

Influence of combining mefloquine with primaquine on the rate of acquisition of resistance to each drug by P. berghei in consecutive passages. Top lines indicate maximum level of primaquine in SP line exposed to primaquine alone. Middle line indicates maximum levels of primaquine and bottom of mefloquine in the mixtures at each passage.

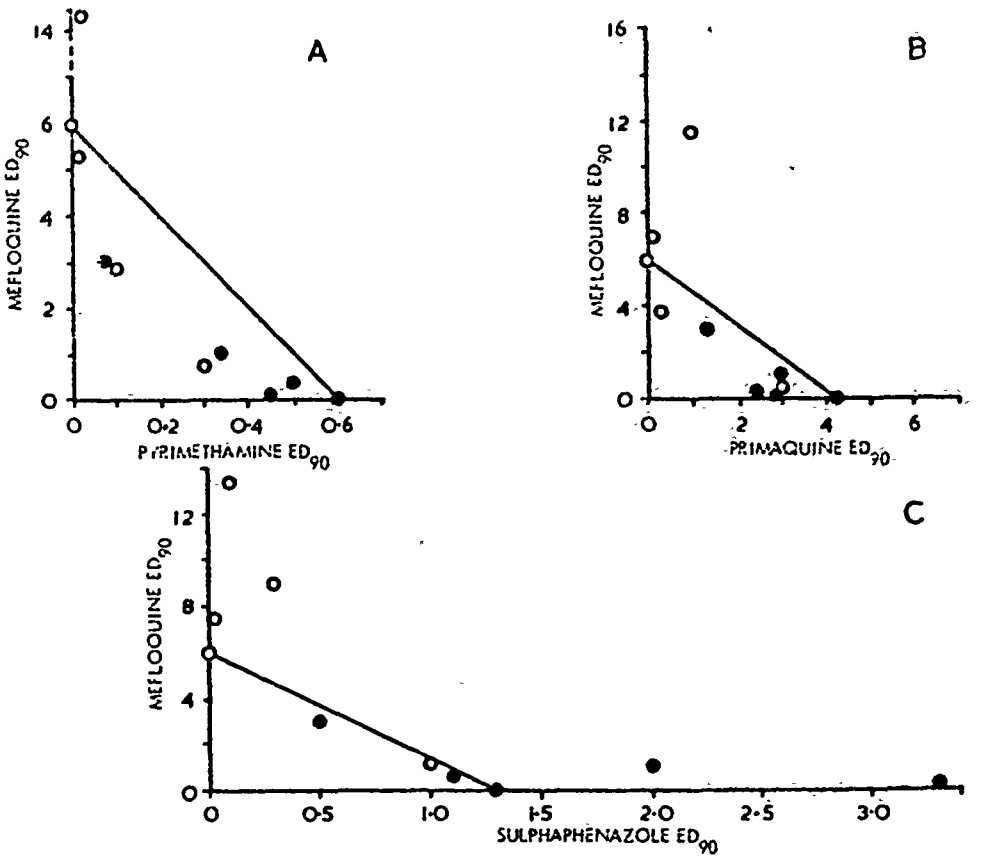

FIGURE 7

Blood schizontocidal action of drug mixtures against P. berghei N strain in the "4 day test". The graphs are plotted to show the ED_{90} values of mefloquine when given alone or with different doses of (A) pyrimethamine, (B) primaquine, or (C) sulphaphenazole (o), or of the latter when given with different doses of mefloquine (•). (All doses in mg/kg daily x 4).

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