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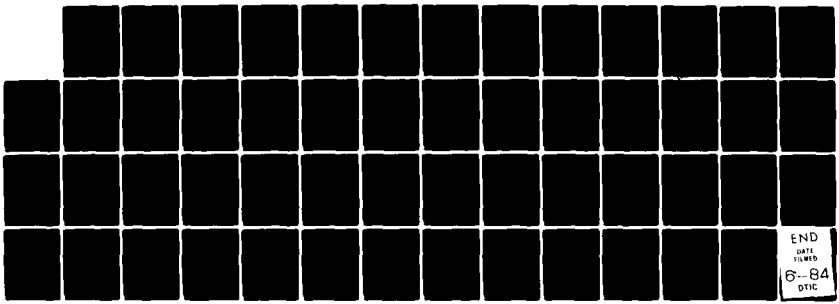

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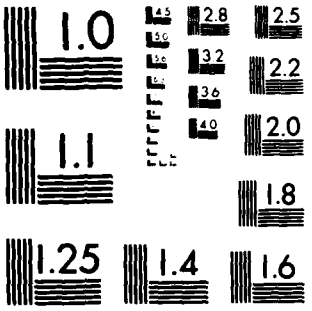

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CHEMOTHERAPY OF RODENT MALARIA

ANNUAL REPORT

by

WALLACE PETERS, MD, DSc

February 1981

Supported by

US ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland 21701

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London School of Hygiene and Tropical Medicine
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TABLE OF CONTENTS

1. INTRODUCTION

This is the first Annual Report to be prepared by the Principal Investigator from his new base in the London School of Hygiene and Tropical Medicine. For administrative reasons the present work in collaboration with WRAIR could only be commenced on September 1st 1980. This Report is entitled "Annual Report" in order to fit in with the cycle of Reports and project grant renewal applications as requested by Dr.Howard E.Noyes in his letter SGRD-UWZ-C dated 9 December 1980, and as clarified with him by telephone on 23 December 1980. This Report therefore only covers our initial 4 months' activities, but includes the completion of experiments carried over from Liverpool and conducted in London prior to the start of this Contract.

2. ADMINISTRATIVE EVENTS

Pending the confirmation of funding from WRAIR under the present contract work was started on the transfer of strains of rodent malaria from the Liverpool collection, and the establishment of laboratory facilities, partly at the main premises in Keppel Street, and partly at the School's field station in Winches Farm, St.Albans (30 miles NE of London). We were fortunate in being able to maintain a close liaison with senior staff of the Division of Experimental Therapeutics at WRAIR through a visit of Colonel Davidson to London, through two visits of the PI to WRAIR, and through several meetings between Colonel Canfield and the PI coinciding with joint service on the Steering Committee of the WHO CHEMAL Scientific Working Group.

Staff employed on US Army funds are as follows:-

Emeritus Professor Dinah James (pharmacologist)	(part-time)
Senior Technologist Mr.B.L.Robinson (ex-Liverpool)	50% time
Trainee Technician Ms.M.West	100% time.

Other staff associated with this project but paid from School sources are:-

Professor W Peters (PI)	20% time
Dr D C Warhurst (Biologist) (Ex-Liverpool)	20% time
Dr D S Ellis (Electron Microscopist)	10% time
Dr W E Ormerod (Biologist-Pharmacologist)	20% time

The conversion of accommodation at Winches Farm originally foreseen for animal accommodation has now been earmarked for insectary and extra laboratory space since (a) WRAIR now requires us to carry out studies on gametocytocidal activity, and (b) animal, but no insectary accommodation has been made available by the School on other funds. However, we still await Local Authority planning permission before we can proceed with the actual building work that should now commence by late February. We have also requested confirmation from the Contracting Officer that the funds allocated in this Contract can be used for this purpose. Pending funding of a parallel project on leishmaniasis the School will advance, in addition to its own major contribution to this minor works operation, the sum that has been requested for the leishmaniasis component.

All WRAIR test compounds have been transferred from Liverpool to London together with all documentation. Since our establishment here we have received from WRAIR a further supply of 28 compounds for testing in various systems. New sources of animal supplies have been established and baseline drug sensitivity data are being established under our new conditions. Supplies of Anopheles stephensi have been made available by courtesy of colleagues in the Ross Institute of the London School.

3. CHEMOTHERAPY STUDIES

3.1 Causal prophylaxis

Pending the establishment of our new insectary facilities, extension of this aspect of our work must remain in abeyance. Cyclically transmissible strains of rodent malaria, however, are maintained in liquid nitrogen ready for use, and a limited number of standard causal prophylactic (CP) tests are currently being run. Data on those compounds examined are appended as Tables 2 through 9, and summarised in Table 1.

The 5-phenoxy substituted 8-aminoquinolines WR 231530 and 232584 are both active, the former so far between 30 and 60 mg/kg sc and po. The latter compound is active between 10 and 30 mg/kg sc with no residual action (RA) at the higher dose, and an MFAD above 30 mg/kg po. The lepidine WR 237222 is inactive at 30 mg/kg po and active from 30 mg/kg sc with no RA at that dose level. The Mannich base WR 225449 is fully active at 30 mg/kg sc and active at that dose po, in both cases with a marked RA. The naphthalene methanol WR232143 is fully active at 10 mg/kg sc with no RA, and active at 30 mg/kg po with some RA. WR 218573, 7295 and 181613 are inactive sc and po at 30 mg/kg.

In order to establish whether compounds that are shown to have a significant residual effect in the CP test (e.g. WR 225449) while appearing, in addition, to have a true CP action, really are acting on the pre-erythrocytic hepatic schizonts, we intend to adopt the techniques developed by Dr.Irène Landau by which she is able to produce massive hepatic infections of P.yoelii in baby rats. This will permit us readily to observe directly any drug action on the tissue schizonts at light and, possibly, ultrastructural level. (Mr.Robinson will visit Dr.Landau's laboratory during January 1981 to study her technique at first hand).

The protocol for our CP test as currently run is enclosed as Appendix 1.

3.2 Gametocytocidal action

For the reasons stated above we have not yet been able to establish routine gametocytocidal screening, but the technique to be employed will be found in Appendix 1. We draw attention to the attached

reprint (Peters and Ramkaran, 1980*) which is relevant to studies on gametocytocides and cyclical transmission of rodent malaria parasites.

3.3 Blood schizontocides

New data obtained with WRAIR compounds in our blood schizontocidal "4-day test" system with sensitive and drug-resistant lines are presented in Tables 11 through 15, and summarised in Table 10. In particular we note that the Mannich base WR 194965 is highly active sc against the N strain, equally active against the NS line but inactive at the MFTD against the RC line. The other Mannich base WR 228258 is somewhat less active sc but more active po against the N strain, and shows a slight loss of activity against the mefloquine-resistant N/1100 line, as in the 8-aminoquinoline WR 225448. This and two others in this series, WR 232584 and 226296 are highly active against the N strain. While WR 232584 and 225448 are only slightly less active against the primaquine-resistant P line, WR 226296 is much less effective against this line.

3.4 Drug combinations

No studies currently being made.

3.5 Development and prevention of drug resistance

In accordance with a request from WRAIR we are in the process of setting up a long-term study to confirm whether the administration of a mixture of mefloquine with Fansidar (pyrimethamine + sulphadoxine) in our hands will inhibit the development of resistance to the individual components as claimed by Merkli et al. (1980).†

3.6 Mode of drug action

Priority has been given to observing the action of three compounds in the chloroquine-induced pigment clumping test (CIPC) of Warhurst. The compounds are the two Mannich bases WR 228258 and WR 194965, and the 8-aminoquinoline WR 225448.

A chloroquine-like mode of action of compounds can be demonstrated in the CIPC test through their influence in promoting the formation of autophagic vacuoles in the Plasmodium trophozoites in vitro. Drugs with a quinine-like action do not induce clumping, and competitively inhibit the action of chloroquine in this test (Warhurst et al., 1974; Warhurst and Thomas, 1975**). Drugs that act in neither manner may inhibit chloroquine-induced clumping non-competitively (or in some cases competitively as in the case of oligomycin, Warhurst and Thomas, 1978**)or may have no

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* See section 4.1

† Merkli, B., Richle, R. and Peters, W. (1980) Ann.trop.Med. Parasit. 74, 1-9.

** Warhurst et al. (1974) Ann.trop.Med.Parasit., 68, 265-281
Warhurst and Thomas (1975) Biochem.Pharmacol., 24, 2047-2056
Warhurst and Thomas (1978) Ann.trop.Med.Parasit., 72, 203

effect at all. Compounds such as the antimetabolites pyrimethamine and sulphadiazine, and the 8-aminoquinolines generally have no effect on CIPC.

In this test we have observed that WR 228258 has a marked chloroquine-like action, its 50% clumping value being 0.00025 mg/ml which is approximately 5 times that for chloroquine diphosphate. Like chloroquine it inhibits clumping at 0.025 mg/ml.

WR 194965 (which is structurally similar to WR 228258 but without the quinoline ring) and the 8-aminoquinoline WR 225448 do not cause pigment clumping at the concentrations tested, but WR 194965 inhibits the clumping caused by chloroquine at a higher concentration. WR 225448 does not.

Thus our preliminary studies would suggest that WR 228258 has a chloroquine-like mode of action and would be unlikely to be effective against highly chloroquine-resistant strains, whereas WR 225448,and possibly WR 194965 would be effective against such resistant parasites. This, however, is not entirely in agreement with the "4-day test" made on these compounds which is reported in section 3.3 above, where it was shown that WR 194965 is inactive against the RC line, but fully active against the NS line. Further tests are being made with these Mannich bases.

Material is at present being prepared for light and electron microscopy to observe the type of morphological changes that are induced in intraerythrocytic P.berghei by these three compounds in vivo. (The action of the compounds on biochemical parameters will also be examined by another member of our team who is supported by other funds.)

3.7 Development of new techniques

As outlined in our original project plans and in our current submission for grant renewal, we shall try to establish a CP test based on the Foley technique. However, in accordance with advice from WRAIR this aspect of our work is receiving a lower priority.

One particularly interesting aspect of our studies that arose during a recent WHO meeting on tissue schizontocides was the lack of correspondence between our data based on the CP test in P.y.nigeriensis, and the data of Dr.Leon Schmidt and others based on studies with P.cynomolgi in the rhesus monkey. In the light of recent discoveries concerning the hypnozoite stage responsible for relapses of P.cynomolgi and, probably also, P.vivax and P.ovale, it is necessary to reorientate our thinking as regards (a) our targets and (b) the interpretation of our experimental data. It seems now more rational to view the pre-erythrocytic schizont (against which true "causal prophylactic" compounds are active, e.g., in rodent malaria) as quite a distinct organism structurally and metabolically from the hypnozoite. With the exception of 6- and 8-aminoquinolines, none of the numerous

chemical groups found to be active in the CP test against rodent malaria have proved to exert an anti-relapse activity against P.cynomolgi. This implies that (a) we should regard the CP test as a model for true causal prophylaxis and test whether compounds active in this are also causally prophylactic against simian parasites (pyrimethamine is a good example - it is a causal prophylactic but not an anti-relapse drug against P.cynomolgi), and (b) we should seek a new model for anti-relapse drugs to replace P.cynomolgi in the rhesus in view of the increasing difficulty in obtaining these monkeys, and their prohibitive cost.

Preliminary work has begun to evaluate the use of the "Dukes minifeeder" (Dukes, et al, 1980*) for comparative studies of the effects of metabolised and unmetabolised compounds against gametocytes and sporogonic stages of Plasmodia. If successful transmission can be consistently achieved by this technique, then it may be possible to extend the gametocytocidal studies to Plasmodium falciparum using gametocytes obtained from culture.

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* Dukes, P., Russel, J., and Nash, S. (1981) Trans.R.Soc.trop.Med.Hyg. (In press)

4. PAPERS PUBLISHED

4.1 Already published

Homewood, C.A. and Neame, K.D. (1980) Biochemistry of malarial parasites. In "Malaria. Vol.1. Epidemiology, chemotherapy, morphology, and metabolism". (Ed.J.P.Kreier). Academic Press, New York. pp.345-405.

Knight, D.J. and Peters, W. (1980) The antimalarial activity of N-benzyloxy-hydrotriazines I. The activity of clociguanil (BRL 50216) against rodent malaria, and studies on its mode of action. Ann.trop.Med. Parasit., 74, 393-404

Merkli, B., Richle, R. and Peters, W. (1980) The inhibitory effect of a drug combination on the development of mefloquine resistance in Plasmodium berghei. Ann.trop.Med.Parasit., 74, 1-9

Peters, W. (1979) Drugs against parasitic diseases. In Pharmaceuticals for developing countries. Conference Proceedings. National Academy of Sciences, Washington DC. pp.59-82.

Peters, W. (1980) Chemotherapy of malaria. In "Malaria, Vol.I. Epidemiology, chemotherapy, morphology, and metabolism" (Ed.J.P.Kreier). Academic Press, New York. pp. 145-283

Peters, W. (1980) Problems of chemotherapy in relation to drug resistance. In Recent advances in malaria research. Proceedings of the International Symposium, New Delhi, November 1977. pp.130-160. Contribution No. 1482.

Peters, W. and Ramkaran, A.E. (1980) The chemotherapy of rodent malaria, XXXII. The influence of p-aminobenzoic acid on the transmission of Plasmodium yoelii and P.berghei by Anopheles stephensi. Ann.trop. Med.Parasit., 74, 275-282. Contribution No. 1535

Seureau, C., Szollosi, A., Boulard, Y., Landau, I. and Peters, W. (1980). Aspects ultrastructureaux de la relation hôe-parasite entre le schizonte de Plasmodium yoelii et la cellular hépatique. Protistologica, 16, 419-426.

4.2 In press

Peters, W. (1981) Pharmacology of antimalarials. In "Manual of chemotherapy of malaria" (Ed.L.J.Bruce-Chwatt). WHO, Geneva.

Schofield, P., Howells,R.E. and Peters, W. (1981) A technique for the selection of long-acting antimalarial compounds using a rodent malaria model. Ann.trop.Med.Parasit. 75,

5. APPENDICES

1. Protocols of test systems

2. Table 1 Summary of causal prophylactic tests against *Plasmodium yoelii nigeriensis*

3 Tables 2 through 9 Details of causal prophylactic tests

4 Table 10 Summary of blood schizontocidal studies in 4-day test against *Plasmoidum berghei*.

5 Tables 11 through 15 Details of 4-day tests of blood schizontocidal action.

6. Reprints
   i Knight and Peters (1980)
   ii Merkli *et al* (1980)
   iii Peters and Ramkaran (1980)

APPENDIX 1

Routine techniques for *in vivo* evaluation of compounds for antimalarial activity

1. General conditions

Eperythrozoon coccoides free, random bred male Swiss white mice (TFW strain, supplied by A.Tuck and Son, Rayleigh, Essex) weighing between 18 and 20 grammes are used for all of the tests.

They are maintained in temperature controlled quarters ($22 \pm 2^{o}C$) in batteries of plastic cages with 5 mice in each cage. The mice are fed Dixon's No. 86 diet and receive tap water *ad libitum*.

2. Parasite species and strains	All *Plasmodium berghei*
1) N (=Keyberg 173)	Sensitive to all routine drugs. No gametocytes. Maintained *in vivo* by syringe passage weekly.
2) NS derived from N	Moderately resistant to chloroquine. Maintained by cyclical passage through *Anopheles stephensi*, and under drug pressure in mice (60 mg/kg sc once during passage).
3) RC derived from N	Highly resistant to chloroquine. Maintained by syringe passage under drug pressure (60 mg/kg sc daily).
4) P derived from N	Highly resistant to primaquine. Maintained by syringe passage under drug pressure (60 mg/kg sc daily).
5) B derived from N	Highly resistant to cycloguanil HCl. Maintained by syringe passage under drug pressure (60 mg/kg sc daily).
6) PYR derived from NK65	Highly resistant to pyrimethamine. Maintained by syringe passage under drug pressure (100 mg/kg ip once during passage).
7) ORA derived from NK65	Highly resistant to sulphonamides. Maintained by syringe passage under drug pressure (1 g/kg sc once during passage, sulphaphenazole).

8)	N/1100 derived from N	Highly resistant to mefloquine. Maintained by syringe passage under drug pressure (60 mg/kg sc once during passage).
9)	N/1086 derived from N	Highly resistant to menoctone. Maintained by syringe passage under drug pressure (60 mg/kg sc daily).
10)	M derived from N	Highly resistant to mepacrine. Maintained by syringe passage under drug pressure (60 mg/kg sc daily).
11)	N67 (= NIG)	P.yoelii nigeriensis. Moderately resistant to chloroquine. Maintained by cyclical passage through A.stephensi without drug pressure.

2. Individual Tests

(A) Blood schizontocidal test

Male random-bred Swiss white mice weighing 18-22 grams are inoculated intravenously with 10^7 parasitised red blood cells of one of the above P.berghei strains. Animals are then teated once daily for four consecutive days beginning on the day of infection. Compounds are dissolved or suspended in Tween 80 and sterile distilled water and administered subcutaneously, intraperitoneally or orally. Where exceptional difficulty is encountered in preparing an aqueous preparation, the test compound is first dissolved in dimethyl sulfoxide and then aqueous dilutions are prepared for use. The parasitaemia is determined on the day following the last treatment and the ED_{50} and ED_{90}, i.e. 50% and 90% suppression of parasites when compared with untreated controls, estimated from plot of log dose: probit activity. Standard error is calculated with the aid of Table 48, Geigy Scientific Tables, 6th edition. The degree of cross resistance is determined by comparing activity in the sensitive and resistant strains.

$$\text{Index of cross resistance } (I_{50} \text{ or } I_{90}) = \frac{ED_{50} \text{ or } ED_{90} \text{ in resistant strain}}{ED_{50} \text{ or } ED_{90} \text{ in sensitive strain}}$$

Notes

1. Peters, W. Drug resistance in Plasmodium berghei, Vincke and Lips, 1948 I. Chloroquine resistance. Expl Parasit., 17, 80-89 (1965)

2. Peters, W., Portus, J.H. and Robinson, B.L. The chemotherapy of rodent malaria, XXII. The value of drug-resistant strains of P.berghei in screening for blood schizontocidal activity. Ann.Trop.Med. Parasit., 69, 155-171 (1975).

3. Amount of compound required: 250-1500 mg depending on active dose level found in preliminary screen.

4. Strains used: N, NS, RC, P, B, PYR, ORA, N/1086, N/1100

(B) Gametocytocidal tests

Mice as described above are used in this test. On day zero (DO) mice are intravenously infected with 10^7 infected red blood cells of the NK65 or NIG strains. On the third day after infection (D+3) the animals are given a single dose of test compound by the subcutaneous or intraperitoneal route of administration. Twelve hours after this drug dose Anopheles stephensi mosquitoes are fed a blood meal for 30 minutes from the treated mice. (Approximately 25 female mosquitoes per mouse are used). On the 7th day after feeding, the mosquitoes are dissected and, using negative phase contrast, oocysts are counted on the individual midguts. Mean oocyst counts of treated animals are compared with those of untreated mice.

Notes

1. Ramkaran, A.E. and Peters, W. Infectivity of chloroquine resistant Plasmodium berghei to Anopheles stephensi enhanced by chloroquine. Nature, Lond., 223, 635-636 (1969)

2. Peters, W. and Ramkaran, A.E. The chemotherapy of rodent malaria, XXXII. The influence of p-aminobenzoic acid on the transmission of Plasmodium yoelii and P.berghei by Anopheles stephensi. Ann. trop.Med.Parasit., 74, 275-282 (1980) Contribution No. 1535

3. Amount of compound required: 50-100 mg.

(C) Sporontocidal test

The same procedure as described in the gametocytocidal test is used, except that only the NK65 strain of P.berghei is employed and the mosquitoes are fed on untreated rather than treated mice. After feeding on the gametocyte carriers the mosquitoes are held in waxed cardboard cartons at 17-21°C, 75% relative humidity and fed solutions of drugs in 4% sucrose supplied in cotton wool pads on top of the gauze covers of the containers. The pads are replaced every other day. Mosquitoes are dissected on the 7th day after the blood meal and the oocysts counted as discussed in the gametocytocidal test.

Notes

1. Ramkaran, A.E. and Peters, W. The chemotherapy of rodent malaria, VIII. The action of some sulphonamides alone or with folic reductase inhibitors against malaria vectors and parasites, part 3: The action of sulphormethoxine and pyrimethamine on the sporogonic stages. Ann.trop.Med.Parasit., 63, 449-454 (1969).

2. Peters, W. and Ramkaran, A.E. The chemotherapy of rodent malaria, XXXII. The influence of p-aminobenzoic acid on the transmission of Plasmodium yoelii, and P.berghei by Anopheles stephensi. Ann. trop.Med. Parasit., 74, 275-282 (1980). Contribution No. 1535

3. Amount of compound required: 50-100 mg.

(D) Preliminary prophylactic screening test

This test, which is a simplified version of the causal prophylactic test, is designed to indicate the presence of any form of prophylactic activity in mice infected with Plasmodium yoelii nigeriensis (N67/NIG).

Three groups of TFW strain mice (three mice/group) are used in this test.

Group I Sporozoite inoculum at DO

Group 2 Sporozoite inoculum at DO; 30 mg/kg test compound at DO + 2 hours

Group 3 Sporozoite inoculum at DO; 100 mg/kg test compound at DO + 2 hours

The sporozoite inoculum is prepared from Anopheles stephensi mosquitoes fed 10-14 days earlier on infected TFW mice. Insects are stunned by concussion and homogenised by hand in a Teflon grinder with TC199 containing 3% w/v Bovine Serum Albumin. The suspension is lightly centrifuged, decanted and 0.2 ml inocula given intravenously. Approximately 300 mosquitoes are used to infect 50 mice. Test compounds are dissolved or suspended in Tween 80 and sterile distilled water and administered subcutaneously, intraperitoneally or orally. Where exceptional difficulty is experienced in making an aqueous preparation, the test compound is first dissolved in dimethyl sulfoxide and then aqueous dilutions are prepared for use. The dose levels used have been arbitrarily selected to give an indication of the doses to be used in the full causal prophylaxis test, and may be varied where necessary, e.g. where the test compound is toxic at the proposed dose.

Stained blood films from each animal are examined at D7 and D14. The results are expressed only as positive or negative and four categories of activity are recognised.

1.	? Fully active	- 0/3 positive
2.	? Active	- 1/3 mice positive
3.	? Slightly active	- 2/3 mice positive
4.	Inactive	- 3/3 mice positive

This preliminary screen affords a simple method of determining the presence or absence of activity, and also by extension of the dose range enables a large number of compounds to be rapidly screened to determine the probably effective dose prior to examination in the full causal prophylactic test.

(E) Causal prophylactic test

This test is designed to differentiate between prophylactic activity and residual suppressive activity of test compounds in mouse malaria infections. The test is based on the inverse linear relationships between the logarithm of the sporozoite inoculum and the mean time taken for the resulting erythrocytic infection rate in groups of mice to reach 2 per cent. This relationship is valid only in an established range and breaks down if (1) the sporozoite inoculum is insufficient to give 100% patency and (2) if the sporozoite inoculum is extremely large. Further, the test depends on the finds that (1) the minimum prepatent period is between 47 and 50 hours (48 hours has been assigned for calculations) and (2) the growth rate and drug sensitivity of the erythrocytic stage of the parasite is independent of the source, i.e. whether derived from injected sporozoites or parasitized red blood cells (rbc).

Five groups of CFW strain mice are routinely used for testing.

They receive:

Group 1 Sporozoite inoculum at DO; saline at DO + 3 hours

Group 2 Sporozoite inoculum at DO; test compound at DO + 3 hours

Group 3	Sporozoite inoculum at DO;	saline at DO + 3 hours; rbc at DO + 48 hours
Group 4	Sporozoite inoculum at DO;	test compound at DO + 3 hours rbc at DO + 48 hours
Group 5	rbc at DO + 48 hours	

The sporozoite inoculum is prepared and administered as described for the preliminary prophylactic screening test.

The blood inoculum from TFW strain mice is given intraperitoneally in a volume of 0.2 ml and consists of 10^7 infected donor red blood cells (rbc) in isotonic saline. The infection is with the NIG (=N67) strain of Plasmodium yoelii nigeriensis.

Test compounds are dissolved and used as previously described for the preliminary screen.

Daily blood films are made and examined from D3 until the parasitaemia reaches 2%. Any animals which do not show patent infection by D14 are considered to be negative. Results are calculated in the manner described by Gregory and Peters (1970).

Differences in the pre-2% patency period between control and treated sporozoite-inoculated animals can reflect a drug action on EE stages, erythrocytic forms or both. Cross-inoculation in parallel series of groups with infected red cells allows the residual drug action on erythrocytic forms to be assessed, leaving a value proportional to the action on the EE stages alone.

Notes

1. Gregory, K.G. and Peters, W. The chemotherapy of rodent malaria, IX. Causal prophylaxis, part I. A method for demonstrating drug action on erythrocytic stages. Ann.trop.Med.Parasit., 64, 15-24 (1970).

2. Peters, W., Davies, E.E. and Robinson, B.L. The chemotherapy of rodent malaria, XXIII. Causal prophylaxis, Part II. Practical experience with Plasmodium yoelii nigeriensis in drug screening. Ann.trop.Med.Parasit., 69, 311-328, (1975).

3. Amount of compound normally required: 500 mg for preliminary plus complete test.

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SUMMARY OF CAUSAL PROPHYLACTIC TEST DATA

	WR No.	LIV No.	Minimum fully active dose (mg/kg x 1)	Residual action at active dose	COMMENT	Type of Compound
BG 94916	231530AA	1533	30-60 s.c.		Preliminary data	8-aminoquinoline
BG 94916	231530AA	1533	30-60 p.o.		Preliminary data	"
BH 57098	237222AA	1613	>30 s.c.	Nil at 30	Active at 30 s.c.	"
BH 57098	237222AA	1613	-	-	Inactive at 30 p.o.	"
BH 05361	232584AA	1541	10-30 s.c.	Nil at 30	Fully active at 30 s.c.	"
BH 05361	232584AA	1541	>30 p.o.	Nil at 30	Active at 30 p.o.	"
BE 66994	218573AA	1543	-	-	Inactive at 30 s.c.	"
BE 66994	218573AA	1543	-	-	Inactive at 30 p.o.	"
BB 49961	7295AD	1556	-	-	Inactive at 30 s.c.	Hydroxyquinoline
BB 49961	7295AD	1556	-	-	Inactive at 30 p.o.	"
BG 62110	181613AB	1557	-	-	Inactive at 30 s.c.	Quinoline methanol
BG 62110	181613AB	1557	-	-	Inactive at 30 p.o.	"
BG 94925	225449AB	1534	10-30 s.c.	Marked at 30	Fully active at 30 s.c. - all activity residual	Mannich base
BG 94925	225449AB	1534	>30 p.o.	Marked at 30	Active at 30 p.o. - all activity residual	"
BH 01069	232143AA	1542	3-10 s.c.	Nil at 10	Fully active at 10 s.c.	Naphthalene
BH 01069	232143AA	1542	>30 p.o.	Present at 30	Active at 30 p.o. - Some residual activity	"

CAUSAL PROPHYLAXIS TEST NO: BR 741 DATE: 26 November 1980

DRUG: 8-aminoquinoline LiV/ 1533 WR 231530AA BOTTLE NO. BG94916

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2 H

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	Prophylactic Activity	
Ø	$5/5$		$5/5$	5.55		3.67				
30.0	$2/3$			>8.91						ACTIVE
60.0	$0/3$			>14						FULLY ACTIVE

MINIMUM FULLY ACTIVE DOSE ..... 30 - 60 ..... mg/kg

RESIDUAL ACTIVITY:

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETER

CAUSAL PROPHYLAXIS TEST NO: BR 741 DATE: 26 November 1980

DRUG: 8-aminoquinoline LIV/ 1533 WR 231530AA BOTTLE NO. BG94916

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/sc~~/po TIME AFTER INFECTION: 2 h

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	Prophylactic Activity	
Ø	$5/_5$		$5/_5$	5.55		3.67				
30.0	$2/_3$			>10.39						ACTIVE
60.0	$0/_3$			>14						FULLY ACTIVE

MINIMUM FULLY ACTIVE DOSE ..30 - 60..... mg/kg

RESIDUAL ACTIVITY: PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

Table 2b

CAUSAL PROPHYLAXIS TEST NO: BR 741 DATE: 26 November 1980

DRUG: 8-aminoquinoline LIV/ 1613 WR 237222 AA BOTTLE NO. BH 57098

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2 Hr

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	Prophylactic Activity	
Ø	$5/_5$	$3/_3$	$5/_5$	5.55	3.65	3.67				
1.0	$3/_3$			5.34					NIL	INACTIVE
3.0	$3/_3$			5.74					NIL	INACTIVE
10.0	$3/_3$		$3/_3$	5.02		3.73		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 10 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

Table 3

CAUSAL PROPHYLAXIS TEST NO: BR 746 DATE: 26 November 1980

DRUG: 8-aminoquinoline LIV/ 1613 WR 237222 AA BOTTLE NO. BH 57098

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2 H

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	Prophylactic Activity	
Ø	$5/_5$	$3/_3$	$3/_3$	4.89	4.59	4.22				
30.0	$2/_3$		$2/_2$	>8.76		4.12		NIL	>3.87	ACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

Table 3b

CAUSAL PROPHYLAXIS TEST NO: BR 741 DATE: 26 November 1980

DRUG: 8-aminoquinoline LIV/ 1613 WR 237222 AA BOTTLE NO. BH 57098

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/sc~~/po TIME AFTER INFECTION: 2 H

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	Prophylactic Activity	
Ø	$5/_5$	$3/_3$	$5/_5$	5.55	3.65	3.67				
3.0	$3/_3$			5.38					NIL	INACTIVE
10.0	$3/_3$			5.53					NIL	INACTIVE
30.0	$3/_3$		$3/_3$	5.54		3.74		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

Table 3c

CAUSAL PROPHYLAXIS TEST NO: BR 720

DRUG: 8-aminoquinoline LiV/ 1541

PREPARATION: Tween 80/H_2O

VERTEBRATE HOST: ♂ TFW MICE

WR 232584AA

ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~

PARASITE (SUB) SPECIES: P. y. nigeriensis

DATE: 26 November 1980

BOTTLE NO. BH05361

TIME AFTER INFECTION: 2 h

STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	Prophylactic Activity	
Ø	$5/_5$	$3/_3$	$5/_5$	5.57	4.45	4.50				
3.0	$3/_3$			6.17					NIL	
10.0	$1/_3$			>11.27					> 5.70	ACTIVE
30.0	$0/_3$		$3/_3$	>14		4.82		NIL	> 8.43	FULLY ACTIVE

MINIMUM FULLY ACTIVE DOSE ..... 10 - 30 ..... mg/kg

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

Table 4a

CAUSAL PROPHYLAXIS TEST NO: BR 720 DATE: 26 November 1980

DRUG: 8-aminoquinoline LIV/ 1541 WR 232584AA BOTTLE NO. BH05361

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/sc~~/po TIME AFTER INFECTION: 2 H

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	Prophylactic Activity	
Ø	$5/_5$	$3/_3$	$5/_5$	5.57	4.45	4.50				
3.0	$3/_3$			5.80					NIL	INACTIVE
10.0	$3/_3$			5.95					NIL	INACTIVE
30.0	$2/_3$		$3/_3$	>8.53		4.39		NIL	>2.96	ACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETER

CAUSAL PROPHYLAXIS TEST NO: BR 728 DATE: 26 November 1980

DRUG: 8-aminoquinoline LIV/ 1543 WR 218573AA BOTTLE NO. BE66994

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2 H

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	Prophylactic Activity	
Ø	$5/_5$	$3/_3$	$5/_5$	4.94	3.80	3.92				
3.0	$3/_3$			5.03					NIL	INACTIVE
10.0	$3/_3$			5.17					NIL	INACTIVE
30.0	$3/_3$		$3/_3$	5.28		3.87		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 s.c. PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

Table 5a

CAUSAL PROPHYLAXIS TEST NO: BR 728 DATE: 26 November 1980

DRUG: 8-aminoquinoline LIV/ 1543 WR 218573AA BOTTLE NO BE66994

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/sc~~/po TIME AFTER INFECTION: 2 h

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	Prophylactic Activity	
Ø	$5/_5$	$3/_3$	$5/_5$	4.94	3.80	3.92				
3.0	$3/_3$			5.18					NIL	INACTIVE
10.0	$3/_3$			5.25					NIL	INACTIVE
30.0	$3/_3$		$3/_3$	6.19		3.86		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

Table 5b

CAUSAL PROPHYLAXIS TEST NO: BR 742

DRUG: Hydroxyquinoline LIV/ 1556 WR 7295AD

PREPARATION: Tween 80/H_2O

VERTEBRATE HOST: ♂ TFW MICE

ROUTE OF ADMINISTRATION: ~~xp/sc/ss~~x

PARASITE (SUB) SPECIES: P. y. nigeriensis

DATE: 26 November 1980

BOTTLE NO. BB49961

TIME AFTER INFECTION: 2 h

STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	Prophylactic Activity	
Ø	$5/_5$	$3/_3$	$5/_5$	5.27	4.00	3.82				
3.0	$3/_3$			5.13					NIL	INACTIVE
10.0	$3/_3$			5.96					NIL	INACTIVE
30.0	$3/_3$			5.13		3.76		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

Table 6a

CAUSAL PROPHYLAXIS TEST NO: BR 742 DATE: 26 November 1980

DRUG: Hydroxyquinoline LiV/ 1556 WR 7295AD BOTTLE NO. BB49961

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/sc~~/po TIME AFTER INFECTION: 2 H

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	Prophylactic Activity	
Ø	$5/_5$	$3/_3$	$5/_5$	5.27	4.00	3.82				
3.0	$3/_3$			4.73					NIL	INACTIVE
10.0	$3/_3$			4.92					NIL	INACTIVE
30.0	$3/_3$		$3/_3$	5.49		3.60		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

Table 6b

CAUSAL PROPHYLAXIS TEST NO: BR742 DATE: 26 November 1980

DRUG: Quinoline methanol LiV/ 1557 WR 181613 AB BOTTLE NO. BG 62110

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/sc/po~~ TIME AFTER INFECTION: 2 H

VERTEBRATE HOST: Ó TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	Prophylactic Activity	
Ø	$5/_5$	$3/_3$	$5/_5$	5.27	4.00	3.82				
3.0	$3/_3$			5.66					NIL	INACTIVE
10.0	$3/_3$			5.01					NIL	INACTIVE
30.0	$3/_3$		$3/_3$	5.95		3.95		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

Table 7a

CAUSAL PROPHYLAXIS TEST NO: BR 742 DATE: 26 November 1980

DRUG: Quinoline methanol LIV/ 1557 WR 181613 AB BOTTLE NO. BG 62110

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/ss~~/po TIME AFTER INFECTION: 2 H

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_T{}^o$	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	Prophylactic Activity	
Ø	$5/_5$	$3/_3$	$5/_5$	5.27	4.00	3.82				
3.0	$3/_3$			4.90					NIL	INACTIVE
10.0	$3/_3$			4.59					NIL	INACTIVE
30.0	$3/_3$			5.04		3.70		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o. PRINCIPAL INVESTIGATOR: PROFESSOR W. PETER

Table 7b

CAUSAL PROPHYLAXIS TEST NO: BR 741 DATE: 26 November 1980

DRUG: Mannich base LiV/ 1534 WR 225449 AB BOTTLE NO. BG94925

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2 Hrs

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	Prophylactic Activity	
Ø	5/5	3/3	5/5	5.55	3.65	3.67				
3.0	2/3			5.24						
10.0	3/3		3/3	5.09		5.26	$-0.46-\left[\frac{1.65 \times 3.26}{1.67}-1.65\right]$	1.58	NIL	INACTIVE
30.0	0/3		2/3	>14		12.10	$>8.45-\left[\frac{1.65 \times 10.10}{1.67}-1.65\right]$	8.34	NIL	FULLY ACTIVE-ALL ACTIVITY RESIDUAL

MINIMUM FULLY ACTIVE DOSE ....10 - 30..... mg/kg

RESIDUAL ACTIVITY: MARKED AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

Table 8a

CAUSAL PROPHYLAXIS TEST NO: BR 741 DATE: 26 November 1980

DRUG: Mannich base LIV/ 1534 WR 225449 AB BOTTLE NO. BG94925

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/sc~~/po TIME AFTER INFECTION: 2 H

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	Prophylactic Activity	
Ø	5/5	3/3	5/5	5.55	3.65	3.67				
10.0	3/3		3/3	6.42		3.79	0.87 -	NIL	0.87	INACTIVE
30.0	3/3		3/3	10.75		8.82	$5.20-\left[\frac{1.65 \times 6.82}{1.67}-1.65\right]$	5.09	0.11	RESIDUAL ACTIVITY ONLY

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

RESIDUAL ACTIVITY: MARKED AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

Table 8b

CAUSAL PROPHYLAXIS TEST NO: BR 728 DATE: 26 November 1980

DRUG: Naphthalene LIV/ 1542 WR 232143AA BOTTLE NO. BH01069

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc/~~po~~ TIME AFTER INFECTION: 2

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NiG

DOSE mg/kg	PATENCY RATE $C^o/_{T^o}$	XC	$C^x/_{T^x}$	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	COMMENT
Ø	$5/_5$		$5/_5$	4.94	3.80	3.92				
3.0	$2/_3$			>8.01		3.86		NIL	> 3.07	SLIGHTLY ACTIVE
10.0	$0/_3$			>14		4.65		NIL	> 9.06	FULLY ACTIVE
30.0	$0/_3$			>14		> 8.76	$>9.06-\left[\frac{1.80 \times >6.76}{1.92}-1.80\right]$	> 4.54	> 7.36	FULLY ACTIVE-SOME RESIDUAL ACTIVITY

MINIMUM FULLY ACTIVE DOSE ..... 3 - 10 ..... mg/kg

RESIDUAL ACTIVITY: NIL AT 10 mg/kg x 1 s.c.
PRESENT AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

Table 9a

CAUSAL PROPHYLAXIS TEST NO: BR 728 DATE: 26 November 1980

DRUG: Naphthalene LIV/ 1542 WR 232143AA BOTTLE NO. BH01069

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/ss~~/po TIME AFTER INFECTION: 2 H

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	f/h	b	c/e	$(h-f)-\left[\frac{(b-c)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	
Ø	$^5/_5$	$^3/_3$	$^5/_5$	4.94	3.80	3.92				
3.0	$^3/_3$			5.38		3.83		NIL	NIL	
10.0	$^2/_3$			>8.08		3.96		NIL	>3.14	SLIGHTLY ACTIVE
30.0	$^1/_3$		$^3/_3$	>11.00		7.65	$>6.06-\left[\frac{1.80 \times 5.65}{1.92}-1.80\right]$	3.50	>2.56	ACTIVE-SOME RESIDUAL ACTIVI

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

RESIDUAL ACTIVITY: PRESENT AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETER

Table 9b

SUMMARY OF BLOOD SCHIZONTOCIDAL (4 DAY TEST) DATA.

L I V No.	Suppliers No.	Route	N		NS		RC		P		B		PYR		ORA		N/1100	
			ED_{50}	ED_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}
1541	WR 232584	sc	0.3	0.5	1.9	3.8	0.4	0.8	2.1	4.2								
	BH 05361	po	0.4	0.6	3.2	5.3	0.9	1.5	2.6	4.3								
1391	WR 226296	sc	0.5	1.2	1.9	1.6	0.6	0.5	26.0	21.7								
	BG 44452	po	0.3	0.5	2.9	5.8	0.7	1.4	7.8	15.6								
LON NO.																		
1707	WR 194965AG	sc	2.2	3.8	4.2	1.1	>MTD	-										
	BG 56327																	
1708	WR 228258AH	sc	4.0	10.0													26.0	2.6
	BJ 30663	po	1.2	2.4													18.0	7.9
1709	WR 225448AG	sc	0.2	0.3	0.8	2.7	0.4	1.3	1.2	4.0							0.4	1.3
	BH 58522	po	0.1	0.2	0.6	3.0	0.6	3.0	1.2	6.0								

ED_{50} / ED_{90} = mg/kg x 4 MTD = maximum tolerated dose

Table 10

SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE IIa

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER WR 232584 BI 05361 ..JJV/1541..... PARASITE (SUB) SPECIES P.b.berghei .....

Route of administration : ~~i.p.~~/s.c./~~p.o.~~

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	0.3	5		-	53.5 ± 5.0
	1.0	5			0
	3.0	5	1	-	0
	10.0	5		-	0
	Ø	10		42.6	
ED_{50} (range)	0.3(0.2-0.4)				
ED_{90} (range)	0.5(0.4-0.6)				
	Resistance factor 90 1.0				
NS	0.3	5		-	78.7 ± 2.8
	1.0	5		-	67.1 ± 2.4
	3.0	5	1	-	2.1 ± 1.2
	10.0	5		-	0
	Ø	10		48.3	
ED_{50} (range)	0.8(0.5-1.4)				
ED_{90} (range)	1.9(1.1-3.2)				
	Resistance factor 90 3.8				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 11b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 232584 / BI 05561 / LIV/1541 ..... PARASITE (SUB) SPECIES: P.b.berghei .....

Route of administration : xxp./s.c./pxxx

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
RC	0.3	5		-	17.2 ± 11.0
	1.0	5		-	0
	3.0	5	1	-	0
	10.0	5		-	0
	Ø	10		3.5	
ED_{50} (range)	0.2(0.1-0.3)				
ED_{90} (range)	0.4(0.3-0.5)				
	Resistance factor 90 0.8				
P	0.3	5		-	67.2 ± 4.1
	1.0	5		-	61.3 ± 5.7
	3.0	5	1	-	28.1 ± 5.7
	10.0	5		-	0
	Ø	10		23.5	
ED_{50} (range)	1.0(0.4-2.2)				
ED_{90} (range)	2.1(0.7-4.7)				
	Resistance factor $_{90}$ 4.2				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 11c

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 232584 / BH 05361 / LIV/1541 ..... PARASITE (SUB) SPECIES: P.b.berghei .....

Route of administration : ~~xxx~~./~~xxx~~./p.o.

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	$\frac{\text{Treated PRS}}{\text{Control PRS}} \times 100$
N	0.3	5		-	71.8 ± 3.6
	1.0	5		-	1.9 ± 0.9
	3.0	5	1	-	0
	10.0	5		-	0
	Ø	10		42.6	
ED_{50} (range)	0.4(0.3-0.4)				
ED_{90} (range)	0.6(0.5-0.8)				
	Resistance factor 90 1.0				
NS	0.3	5		-	76.6 ± 2.0
	1.0	5		-	75.0 ± 4.4
	3.0	5	1	-	46.8 ± 7.6
	10.0	5		-	0
	Ø	10		48.3	
ED_{50} (range)	1.9(1.1-3.0)				
ED_{90} (range)	3.2(1.9-5.1)				
	Resistance factor 90 5.3				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 11d

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER WR 252584 BH 05561 ..LIV/1541..... PARASITE (SUB) SPECIES..P.b.berghei.....

Route of administration : ~~oral~~/~~s.c.~~/p.o.

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
RC	0.3	5		-	51.4 ± 16.5
	1.0	5		-	40.0 ± 16.5
	3.0	5	1	-	0
	10.0	5		-	0
	Ø	10		3.5	
ED_{50} (range)	0.5(0.2-1.0)				
ED_{90} (range)	0.9(0.5-1.8)				
	Resistance factor 90 1.5				
P.	0.3	5		-	78.3 ± 2.5
	1.0	5		-	66.4 ± 5.7
	3.0	5	1	-	51.1 ± 3.3
	10.0	5		-	0
	ψ	10		23.5	
ED_{50} (range)	1.3(0.5-3.3)				
ED_{90} (range)	2.6(0.9-6.2)				
	Resistance factor 90 4.3				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 12a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 226296 / BJ 44452 / LIV/1391 ..... PARASITE (SUB) SPECIES: P.b.berghei .....

Route of administration : ~~i.v.~~/s.c./~~p.o.~~

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	Treated PRS / Control PRS x 100
N	0.3	5		-	69.0 ± 2.7
	1.0	5		-	4.2 ± 1.8
	3.0	5	1	-	2.1 ± 0.9
	10.0	5		-	0
	Ø	10		42.6	
ED_{50} (range)	0.5(0.2-0.6)				
ED_{90} (range)	1.2(0.6-1.8)				
	Resistance factor 90 1.0				
NS	0.3	5		-	71.2 ± 2.8
	1.0	5		-	66.3 ± 3.6
	3.0	5	1	-	15.3 ± 5.6
	10.0	5		-	
	Ø	10		48.3	
ED_{50} (range)	0.8(0.4-1.7)				
ED_{90} (range)	1.9(1.0-4.0)				
	Resistance factor $_{90}$ 1.6				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 12b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 226296 BI 44452 LIV/1391 ..... PARASITE (SUB) SPECIES: P.b.berghei .....

Route of administration : ~~i.p.~~/s.c./~~p.o.~~

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	Treated PRS / Control PRS x 100
RC	0.3	5		-	91.4 ± 27.4
	1.0	5		-	0
	3.0	5	1	-	0
	10.0	5		-	0
	Ø	10		3.5	
ED_{50} (range)	0.4(0.3-0.7)				
ED_{90} (range)	0.6(0.4-0.9)				
	Resistance factor 90 0.5				
P	0.3	5		-	95.3 ± 4.9
	1.0	5		-	87.7 ± 3.3
	3.0	5	1	-	75.8 ± 7.4
	10.0	5		-	32.3 ± 6.5
	Ø	10		23.5	
ED_{50} (range)	4.6(1.8-10.0)				
ED_{90} (range)	26 (10-56)				
	Resistance factor $_{90}$ 21.7				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 12c

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 226296 BI 44452 LIV/1391 ..... PARASITE (SUB) SPECIES: P.b.berghei

Route of administration : ~~i.v./s.c.~~/p.o.

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	0.3	5		-	54.5 ± 7.8
	1.0	5		-	0
	3.0	5	1	-	0
	10.0	5		-	0
	Ø	10		42.6	
ED_{50} (range)	0.3(0.2-0.4)				
ED_{90} (range)	0.5(0.4-0.6)				
	Resistance factor 90 1.0				
NS	0.3	5		-	73.7 ± 2.4
	1.0	5		-	72.1 ± 3.2
	3.0	5	1	-	19.5 ± 5.2
	10.0	5		-	0
	Ø	10		48.3	
ED_{50} (range)	1.6(1.2-2.2)				
ED_{90} (range)	2.9(2.2-4.0)				
	Resistance factor 90 5.8				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 12d

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER WR 226296 BU 44452 LIV/1391 ..... PARASITE (SUB) SPECIES P.b.berghei .....

Route of administration : ~~xxxxxxxx~~/p.o.

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
RC	0.3	5		-	34.3 ± 11.0
	1.0	5		-	11.4 ± 5.5
	3.0	5	1	-	0
	10.0	5		-	0
	Ø	10		3.5	
ED_{50} (range)	0.3(0.2-0.6)				
ED_{90} (range)	0.7(0.4-1.2)				
	Resistance factor 90 1.4				
P	0.3	5		-	61.3 ± 7.4
	1.0	5		-	58.7 ± 2.5
	3.0	5	1	-	51.9 ± 4.1
	10.0	5		-	8.5 ± 3.3
	Ø	10		23.5	
ED_{50} (range)	1.4(0.4-3.8)				
ED_{90} (range)	7.8(2.0-22.0)				
	Resistance factor 90 15.6				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 13a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 194965 AG, BG 56327, LON 1707 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : ~~x~~p./s.c./~~p~~o~~x~~

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	1.0	5		-	95.0 ± 3.0
	3.0	5		-	39.0 ± 6.2
	10.0	5	1	-	0
	Ø	10		53.0	
ED_{50} (range)	2.2(1.8-2.8)				
ED_{90} (range)	3.8(3.1-4.7)				
	Resistance factor 90 1.0				
NS	1.0	5		-	98.0 ± 3.6
	3.0	5		-	40.0 ± 5.6
	10.0	5	1	-	0.05 ± 0.05
	30.0	5		-	0
	Ø	10		46.0	
ED_{50} (range)	2.4(1.9-3.0)				
ED_{90} (range)	4.2(3.2-5.0)				
	Resistance factor 90 1.1				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 15b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 194965 / BG 56327 / LON 1707 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration :xixpx/s.c./pxpx

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	Treated PRS / Control PRS x 100
RC	3.0	5		-	98.5 ± 4.5
	10.0	5		-	95.0 ± 3.2
	30.0	5	1	-	84.0 ± 4.3
	100.0	5		-	>LD 100
	Ø	10		6.2	
ED_{50} (range)	> MTD				
ED_{90} (range)	>> MTD				
	Resistance factor 90				
ED_{50} (range)					
ED_{90} (range)					
	Resistance factor 90				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 14a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 228258 AH, BJ 30663, LON 1708 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : ~~xxx~~/s.c./~~xxx~~

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	1.0	5		-	95.3 ± 5.9
	3.0	5		-	83.6 ± 7.7
	10.0	5	1	-	7.8 ± 3.6
	30.0	5		-	0.2 ± 0.1
	Ø	10		37.6	
ED_{50} (range)	4.0(2.6-6.7)				
ED_{90} (range)	10.0(7.0-17.0)				
	Resistance factor 90 1.0				
N/1100	1.0	5		-	85.0 ± 10.0
	3.0	5		-	51.3 ± 15.9
	10.0	5	2	-	39.0 ± 5.2
	30.0	10		-	33.1 ± 5.4
	100.0	5		-	0
	Ø	10		17.7	
ED_{50} (range)	13.0(7.5-23.0)				
ED_{90} (range)	26.0(15.0-44.0)				
	Resistance factor $_{90}$ 2.6				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 14b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 228258AH, BJ 30663, LON 1708 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : ~~XXXXXXXXX~~/p.o.

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	1.0	5		-	54.0 ± 15.0
	3.0	5		-	15.4 ± 11.2
	10.0	5	1	-	0
	Ø	10		37.6	
ED_{50} (range)	1.2(0.9-1.7)				
ED_{90} (range)	2.4(1.0-3.4)				
	Resistance factor 90 1.0				
N/1100	1.0	5		-	88.4 ± 7.2
	3.0	5		-	56.3 ± 6.9
	10.0	5	2	-	49.1 ± 11.4
	30.0	10		-	27.9 ± 9.0
	100.0	5		-	0
	Ø	10		17.7	
ED_{50} (range)	9.5(4.4-24.0)				
ED_{90} (range)	18.0(8.0-40.0)				
	Resistance factor 90 7.9				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 15a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 225448AG / BH 58522 / LON 1709 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : oral/s.c./p.o.

Strain	Daily dose mg/kg D0 - D+3	No.of mice	No.of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	0.1	5		-	87.5 ± 5.2
	0.3	5		-	4.5 ± 1.0
	1.0	5	1	-	0
	3.0	5		-	0
	Ø	10		42.5	
ED_{50} (range)	0.2(0.1-0.2)				
ED_{90} (range)	0.3(0.2-0.3)				
	Resistance factor 90 1.0				
NS	0.1	5		-	96.5 ± 8.5
	0.3	5		-	87.8 ± 4.8
	1.0	5	1	-	5.1 ± 2.3
	3.0	5		-	0
	Ø	10		57.4	
ED_{50} (range)	0.4(0.2-0.6)				
ED_{90} (range)	0.8(0.3-1.1)				
	Resistance factor 90 2.7				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 15b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 225448AG / BJ 58522 / LON 1709 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : ~~oral~~/s.c./~~i.v.~~

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
RC	0.1	5		-	98.1 ± 7.5
	0.3	5		-	60.0 ± 8.4
	1.0	5	1	-	0
	3.0	5		-	0
	Ø	10		4.1	
ED_{50} (range)	0.3(0.2-0.4)				
ED_{90} (range)	0.4(0.3-0.6)				
	Resistance factor 90 1.3				
P	0.1	5		-	82.7 ± 6.5
	0.3	5		-	66.4 ± 12.0
	1.0	5	1	-	21.2 ± 4.6
	3.0	5		-	1.3 ± 0.4
	Ø	10		20.8	
ED_{50} (range)	0.3(0.2-0.7)				
ED_{90} (range)	1.2(0.8-2.4)				
	Resistance factor $_{90}$ 4.0				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 15c

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 225448 AG / BI 58522 / LON 1709 ..... PARASITE (SUB) SPECIES...P.bergbei.....

Route of administration : ~~oxxx~~/s.c./~~Rx0x~~

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	$\frac{\text{Treated PRS}}{\text{Control PR\%}} \times 100$
N/1100	0.1	5		-	68.0 ± 7.7
	0.3	5		-	48.1 ± 13.1
	1.0	5	1	-	0.1 ± 0.1
	3.0	5		-	0
	Ø	10		23.0	
ED_{50} (range)	0.2(0.1-0.4)				
ED_{90} (range)	0.4(0.2-0.7)				
	Resistance factor 90 1.3				
ED_{50} (range)					
ED_{90} (range)					
	Resistance factor 90				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 15d

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 225448 AG; BH 58522; LON 1709 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : ~~XXP~~/~~SXXX~~/p.o.

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	0.1	5		-	65.5 ± 19.2
	0.3	5		-	2.9 ± 0.8
	1.0	5	1	-	0.01 ± 0.01
	3.0	5		-	0
	Ø	10		42.5	
ED_{50} (range)	0.1(0.1-0.2)				
ED_{90} (range)	0.2(0.2-0.3)				
	Resistance factor 90 1.0				
NS	0.1	5		-	89.9 ± 4.2
	0.3	5		-	69.0 ± 4.7
	1.0	5	1	-	1.1 ± 0.4
	3.0	5		-	0
	Ø	10		57.4	
ED_{50} (range)	0.3(0.2-0.4)				
ED_{90} (range)	0.6(0.4-1.0)				
	Resistance factor 90 3.0				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 15e

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 225448 AG / BH 58522 / LON 1709 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : ~~xxx~~/~~xxx~~/p.o.

Strain	Daily dose mg/kg DO - D+3	No.of mice	No.of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
RC	0.1	5		-	96.6 ± 8.0
	0.3	5		-	60.0 ± 10.8
	1.0	5	1	-	0.7 ± 0.5
	3.0	5		-	0
	ø	10		4.1	
ED_{50} (range)	0.3(0.2-0.4)				
ED_{90} (range)	0.6(0.4-0.8)				
	Resistance factor 90 3.0				
P	0.1	5		-	79.8 ± 10.0
	0.3	5		-	51.9 ± 11.1
	1.0	5	1	-	22.1 ± 2.8
	3.0	5		-	1.0 ± 0.4
	ø	10		20.8	
ED_{50} (range)	0.3(0.2-0.5)				
ED_{90} (range)	1.2(0.6-1.9)				
	Resistance factor 90 6.0				

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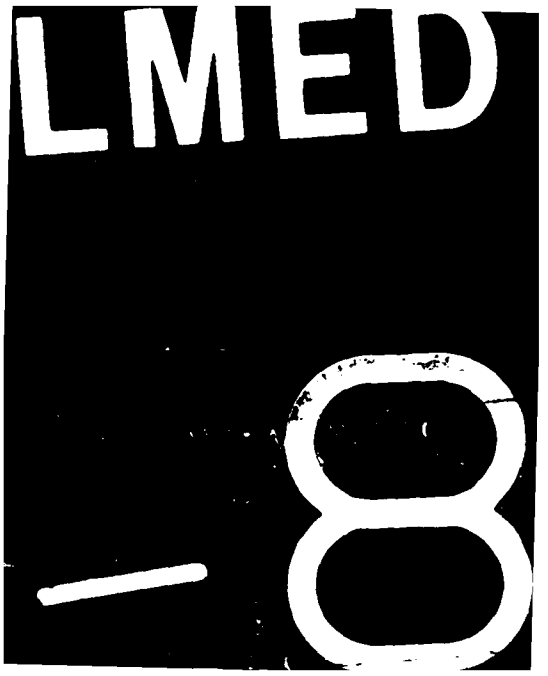
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