Drugs of the Future 2003, 28(9): 859-869

CCC: 0377-8282/2003

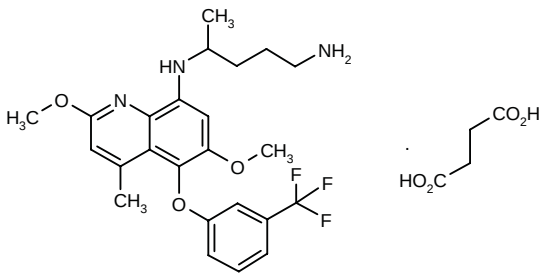
Tafenoquine Succinate

Antimalarial

Prop INNM

SB-252263
WR-238605

(±)-8-(4-Amino-1-methylbutylamino)-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline succinate
(±)-2,6-Dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]primaquine succinate
(±)-N^4-[2,6-Dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]-8-quinolinyl]-1,4-pentanediamine butanedioate



$C_{24}H_{28}F_3N_3O_3.C_4H_6O_4$
Mol wt: 581.5846
CAS: 106635-81-8
CAS: 106635-80-7 (as free base)
EN: 163660

Abstract

Malaria is a significant public health problem in developing and third world countries. *Plasmodium falciparum* and *Plasmodium vivax* parasites are responsible for the majority of cases of malaria infection. Treatment focuses on both chemoprevention and treatment of acute infection, but the currently used drugs are threatened by drug-resistant species in many parts of the world. Tafenoquine is a new 8-aminoquinoline with an improved therapeutic index and safety profile as compared to primaquine. In pharmacological studies, tafenoquine has been shown to be at least 10 times more potent than primaquine and has a much longer half-life, allowing less frequent dosing in chemoprophylactic regimens. Its clinical efficacy has been demonstrated in a number of studies, both as a chemoprophylactic agent for the prevention of *P. falciparum* infection and as an acute treatment against the liver stages of *P. vivax*. Tafenoquine has the potential to become a widely used drug in the prevention and treatment of malaria infection and could replace some currently used drugs as resistant strains of *Plasmodium* species increase.

Synthesis

Chlorination of 6-methoxy-4-methylquinolin-2(1*H*)-one (I) with SO_2Cl_2 in hot acetic acid gives the 5-chloro derivative (II), which is nitrated with HNO_3 in H_2SO_4 to yield the 8-nitroquinolinone (III). Condensation of compound (III) with 3-(trifluoromethyl)phenol (IV) by means of KOH in NMP provides the diaryl ether (V), which is treated with refluxing $POCl_3$ to afford the 2-chloroquinoline (VI). Reaction of compound (VI) with MeONa in refluxing methanol results in the 2,6-dimethoxyquinoline derivative (VII), which is reduced with hydrazine over Pd/C to give the 8-aminoquinoline derivative (VIII) (1). Condensation of aminoquinoline (VIII) with *N*-(4-iodopentyl)phthalimide (IX) by means of diisopropylamine in hot NMP yields the phthalimido precursor (X), which is finally cleaved with hydrazine in refluxing ethanol (1-3). Scheme 1.

Some of the intermediates in the synthesis of tafenoquine can be prepared by several alternative ways.

N-(4-Iodopentyl)phthalimide (IX):

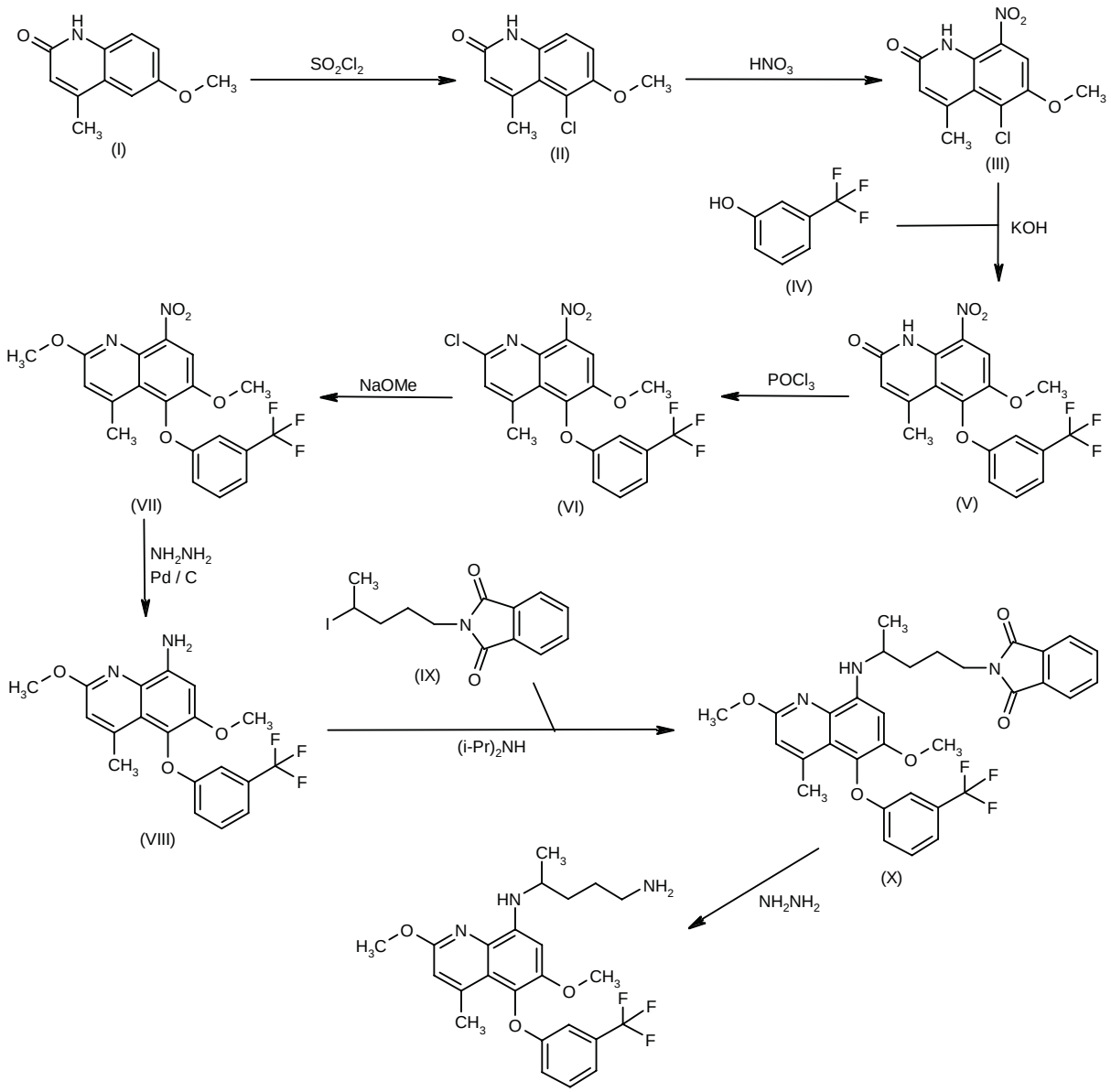
Reaction of 1,4-dibromopentane (XI) with potassium phthalimide (XII) gives *N*-(4-bromopentyl)phthalimide (XIII), which is then treated with NaI in refluxing acetone (1). Scheme 2.

8-Amino-2,6-dimethoxy4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline (VIII):

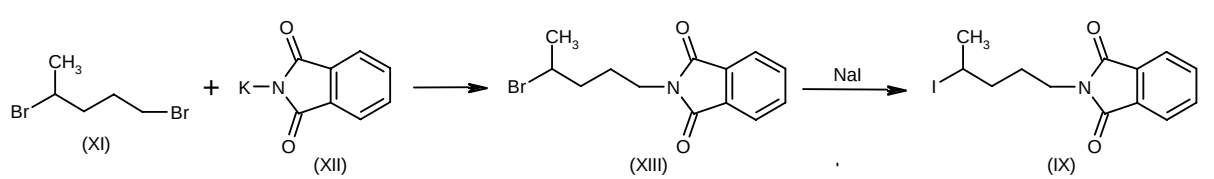
a) Reaction of 8-amino-6-methoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline (XIV) with phthalic anhydride (XV) affords the phthalimido derivative (XVI), which is oxidized with MCPBA to yield the quinoline *N*-oxide (XVII). Treatment of compound (XVII) with neutral alumina gives the quinolone derivative (XVIII), which by reaction with $POCl_3$ in refluxing $CHCl_3$ provides the 2-chloroquinoline derivative (XIX). Alternatively, reaction of the quinoline *N*-oxide (XVII) with $POCl_3$ as before also gives the 2-chloroquinoline derivative (XIX) The removal of the phthalimido group of compound (XIX) by means of

J.A. McIntyre, J. Castañer, M. Bayés. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

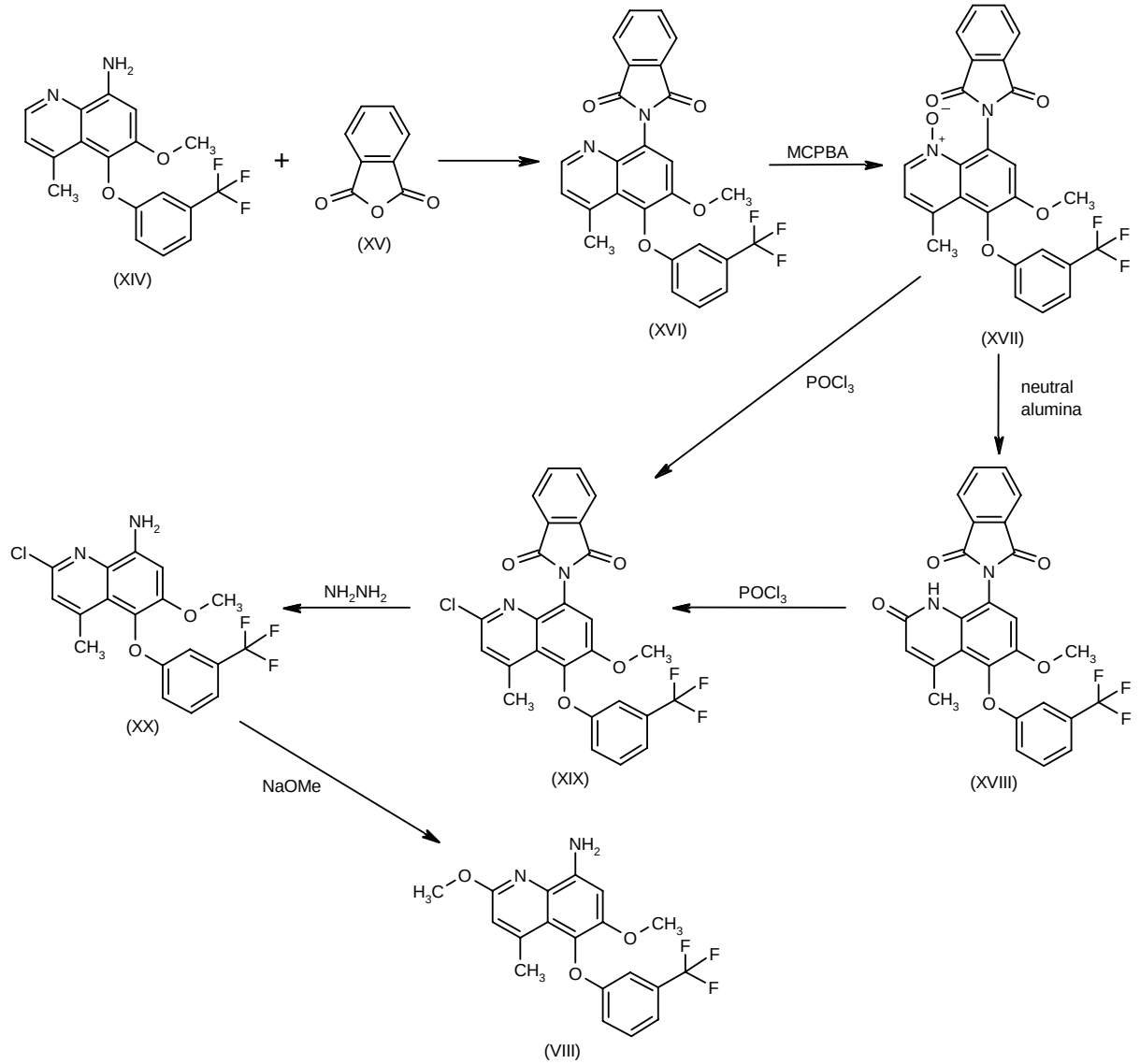
Scheme 1: Synthesis of Tafenoquine



Scheme 2: Synthesis of Intermediate (IX)



Scheme 3: Synthesis of Intermediate (VIII)



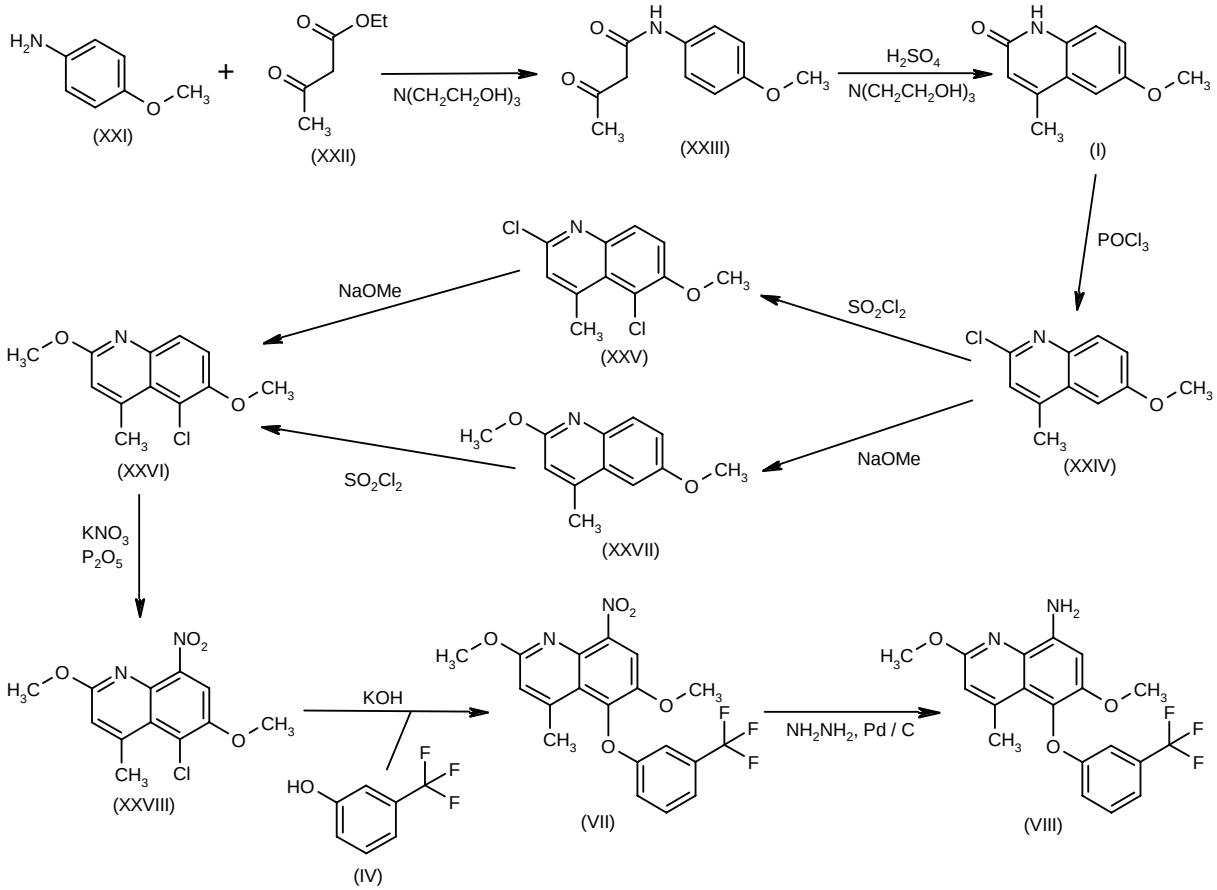
hydrazine in refluxing ethanol gives the chlorinated aminoquinoline (XX), which is finally treated with MeONa in hot DMF (2, 3). Scheme 3.

b) Reaction of 4-methoxyaniline (XXI) with ethyl acetoacetate (XXII) by means of triethanolamine in refluxing xylene gives the acetoacetanilide (XXIII), which is cyclized by means of hot triethanolamine and H_2SO_4 to yield 6-methoxy-4-methylquinolin-2(1*H*)-one (I), which is treated with refluxing $POCl_3$ to provide 2-chloro-6-methoxy-4-methylquinoline (XXIV). Reaction of compound (XXIV) with SO_2Cl_2 in hot AcOH affords 2,5-dichloro-6-methoxy-4-methylquinoline (XXV), which is treated with MeONa in refluxing methanol to furnish 5-chloro-2,6-dimethoxy-4-methylquinoline (XXVI). Alternatively, the reaction of compound (XXIV) with MeONa as before gives 2,6-dimethoxy-4-methylquinoline (XXVII), which is treated with SO_2Cl_2 in hot AcOH to give the already described 5-chloro-2,6-dimethoxy-4-methylquinoline (XXVI). Nitration of compound (XXVI) with KNO_3 and P_2O_5 gives the 8-nitroquinoline derivative (XXVIII), which is condensed with 3-(trifluoromethyl)phenol (IV) by means of KOH in hot NMP to yield the diaryl ether (VII). Finally, the nitro group of compound (VII) is reduced with hydrazine over Pd/C (1). Scheme 4

8-Amino-6-methoxy-4-methyl-5-[3-(trifluoromethyl)-phenoxy]quinoline (XIV):

a) Nitration of 1,2-dimethoxybenzene (XXIX) with HNO_3/AcOH gives 4,5-dimethoxy-1,2-dinitrobenzene (XXX), which is treated with ammonia in hot methanol to yield 4,5-dimethoxy-2-nitroaniline (XXXI). Cyclization of

Scheme 4: Synthesis of Intermediate (VIII)



compound (XXXI) with buten-2-one (XXXII) by means of H_3PO_4 and H_3AsO_4 affords 5,6-dimethoxy-4-methyl-8-nitroquinoline (XXXIII) (4), which is selectively monodemethylated by means of HCl in ethanol to provide 5-hydroxy-6-methoxy-4-methyl-8-nitroquinoline (XXXIV). Reaction of quinoline (XXXIV) with $POCl_3$ gives the corresponding 5-chloro derivative (XXXV), which is condensed with 3-(trifluoromethyl)phenol (IV) by means of KOH to yield the diaryl ether (XXXVI). Finally, the nitro group of (XXXVI) is reduced by means of H_2 over PtO_2 in THF (3) or H_2 over Raney nickel (5). Scheme 5.

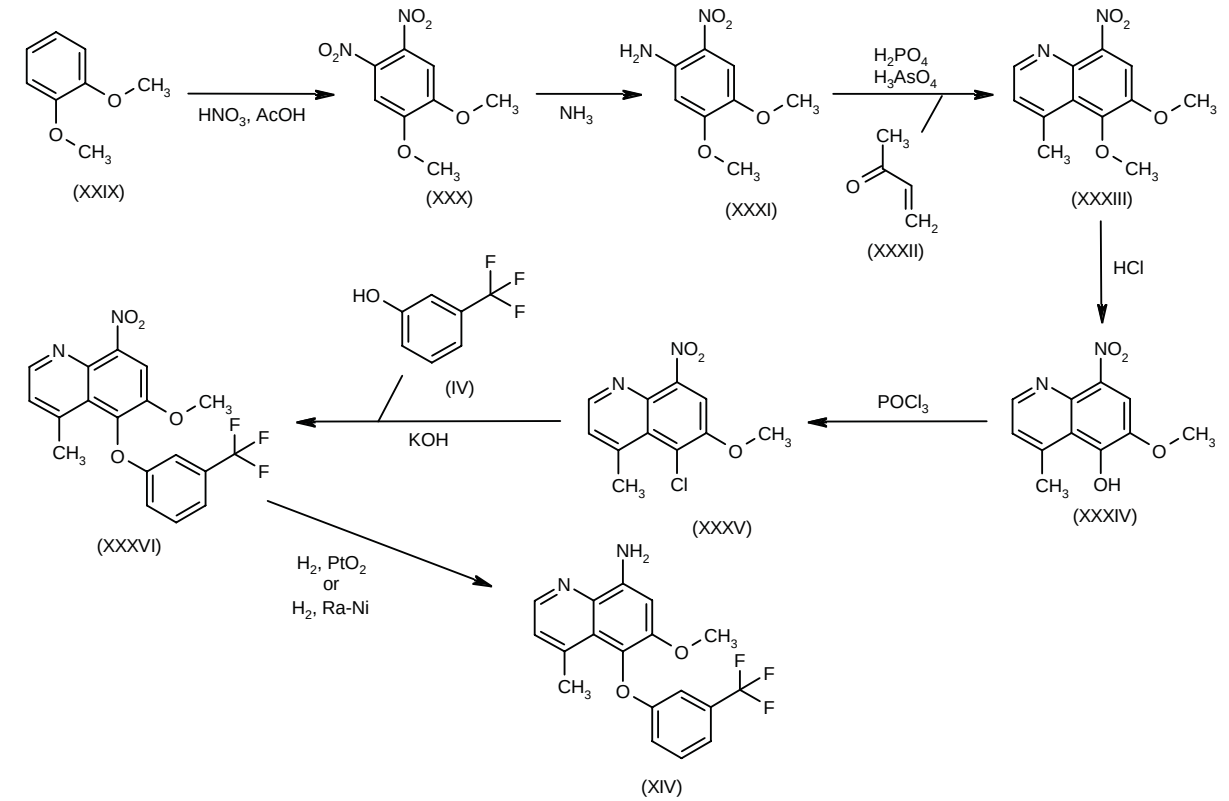
b) Nitration of 2-fluoroanisole (XXXVII) with HNO_3/Ac_2O gives 3-fluoro-4-methoxynitrobenzene (XXXVIII), which is reduced to the corresponding aniline (XXXIX) with $SnCl_2$/HCl. Reaction of compound (XXXIX) with Ac_2O yields the acetanilide (XL), which is nitrated with HNO_3 to afford 5-fluoro-4-methoxy-2-nitroacetanilide (XLI). Hydrolysis of (XLI) with NaOH provides 5-fluoro-4-methoxy-2-nitroaniline (XLII), which is cyclized with buten-2-one (XXXII) by means of As_2O_5 and H_3PO_4 to furnish 5-fluoro-6-methoxy-4-methyl-8-nitroquinoline (XLIII). Condensation of quinoline (XLIII) with 3-(trifluoromethyl)phenol (IV) by means of K_2CO_3 gives the diaryl ether (XXXIV), which is finally reduced by means of H_2 over PtO_2 in THF (4). Scheme 6.

Introduction

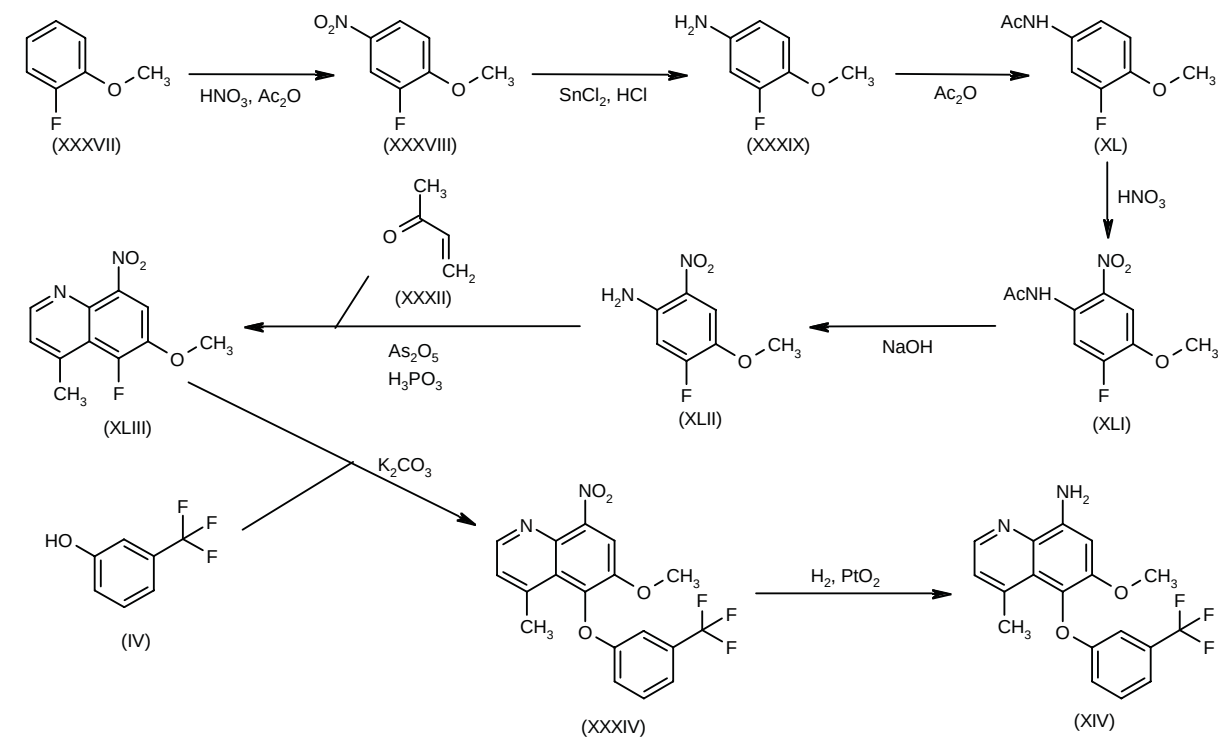
Malaria is a significant public health problem in developing and third world countries. There are over 300 million cases and 1-2 million deaths annually in these regions. Sub-Saharan Africa accounts for 90% of the worldwide malaria burden and up to 0.86 million African infants up to the age of 4 years die each year. Therapeutic intervention focuses on 2 aspects: the treatment of acute malaria and its prevention by chemoprophylaxis. The parasite responsible for the majority of deaths is *Plasmodium falciparum*, but *Plasmodium vivax* also accounts for considerable morbidity; these two parasites are responsible for the majority of cases of malaria infection.

Drugs active against malaria are defined by the stage of the life cycle of the parasite on which they act.

Scheme 5: Synthesis of Intermediate (XIV)



Scheme 6: Synthesis of Intermediate (XIV)



Chloroquine was the most widely used blood schizontocide, acting upon intraerythrocytic schizogony, while primaquine is active against the secondary exoerythrocytic schizogony (liver stage) of both *P. vivax* and *Plasmodium ovale* and is used for the radical cure of these parasites. Primaquine belongs to the class of drugs known as the 8-aminoquinolines, which are active against the liver stages of *Plasmodium* species. This has been the drug of choice to eliminate latent liver forms of *P. vivax* and *P. ovale* and has also been used as prophylaxis against *P. falciparum*. However, multidrug resistance has developed, requiring newer antimalarials, both as chemoprophylaxis and for the treatment of established infections (6, 7).

Pharmacological Actions

The sporontocidal activity of tafenoquine against Plasmodium berghei has been demonstrated in several studies using a cloned line of *P. berghei* ANKA in *Anopheles stephensi* mosquitoes (8-10). One of the studies showed that the *P. berghei* model could be used to accurately predict sporontocidal activity against *P. falciparum* (10).

In a rodent model, tafenoquine was about 9 times as active as primaquine against the asexual, intraerythrocytic stages of drug-sensitive *P. berghei* N strain and from 4-100 times as active as primaquine against lines of *P. berghei* or *Plasmodium yoelii* that were resistant to currently used antimalarials (11).

The efficacy of tafenoquine against the blood schizontocidal activity of a chloroquine-resistant strain of *P. vivax* was demonstrated in *Aotus* monkeys. Monkeys received either 0.8 or 3.2 mg base/kg/day for 3 days. The study showed that tafenoquine acted slowly against the asexual blood stages of this strain of *P. vivax*. This activity, in addition to its tissue schizontocidal activity, supported the indication for its use in the radical cure of *P. vivax* infections in travelers returning from malarious areas (12). A further study in *Aotus* monkeys also investigated the schizontocidal activity of tafenoquine and chloroquine, alone and in combination, against a chloroquine-resistant strain of *P. vivax* (AMRU 1). A total dose of 9 mg/kg of tafenoquine over 3 days cured infections in all monkeys. Although total doses of 30 mg/kg of chloroquine and 3 mg/kg of tafenoquine alone failed to cure, the two drugs given in combination at these doses cured 2 of 3 infections, indicating an additive effect of the drugs (13).

In rhesus monkeys, tafenoquine administered at a dose of 3.16 mg(base)/kg/day for 7 days cured established trophozoite-induced infections in monkeys with *Plasmodium cynomolgi* B and *Plasmodium fragile* simian parasite infections. A lower dose of 1.0 mg/kg/day cured 75% of the *P. cynomolgi* and 91% of *P. fragile* infections. In this study, tafenoquine was at least 10 times more effective than primaquine 10 mg/kg/day, which provided only 25% and 66% protection against *P. cynomolgi* and *P. fragile*, respectively. These two parasites are recognized as biological counterparts of *P. vivax* and *P. falciparum* infections in humans, respectively (14).

The activity of tafenoquine has also been investigated in combination with halofantrine. In the *P. cynomolgi* rhesus monkey relapsing malaria model, tafenoquine 3.16 mg/kg/day and halofantrine 10 mg/kg/day as individual regimens, were curative against blood schizontocides. Doses of 0.316 mg/kg/day and 3.16 mg/kg/day, respectively, as a combined therapy were also curative, as were these doses in the radical curative test. These results indicated that the combination therapy of tafenoquine and halofantrine was potentially synergistic against the blood stage of the infection and that the combination therapy was warranted (15).The significant blood stage activity of tafenoquine has also been demonstrated *in vitro* in a panel of *P. falciparum* isolates (16).

In addition to its efficacy against *Plasmodium* species, tafenoquine has also been shown to be effective both *in vitro* and *in vivo* in rat models for the treatment and prophylaxis of *Pneumocystis carinii* (17-19). In hamsters infected with *Babesia microti*, tafenoquine also produced clearance of patent parasitemia and produced a parasitologic cure (20).

Pharmacokinetics and Metabolism

The pharmacokinetics of tafenoquine have been reported in rats using radiolabeled [^{14}C]-tafenoquine 5 mg/kg. Peak blood levels of unchanged drug were reached at 9 h and the elimination half-life was 3.1 days. Five percent of the total dose was eliminated in the urine, while 75% of total [^{14}C] was eliminated in the feces by 324 h, of which 95% was unchanged drug (21). A combined pharmacokinetic-pharmacodynamic model was also developed to predict mean peak plasma levels of tafenoquine using beagle dogs (22).

In the first-time-in-humans randomized, double-blind, placebo-controlled study, 48 men were administered single oral doses of tafenoquine ranging from 4-600 mg (base). Linear kinetics were demonstrated over the range of doses studied and the data was best described by a one-compartment model with first-order absorption and elimination. Tafenoquine was slowly absorbed and metabolized, with a t_{max} of 12 h and an elimination half-life of 14 days. In this study, the half-life of tafenoquine was more than 50 times longer than that previously observed for primaquine (23). The results of this study and some that follow are summarized in Table I.

The pharmacokinetics of tafenoquine were also studied in 12 volunteers, in a pilot, placebo-controlled, multiple-dose prophylactic challenge study. In this study, t_{max} was 12 h and the elimination half-life was 21.5 days (24).

The population pharmacokinetics of tafenoquine were described in 135 male Thai soldiers who received the drug for malaria prophylaxis. In this study, utilizing sparse data from field conditions, t_{max} was 8.6 h and the elimination half-life was 16.4 days (7).

Clinical Studies

In a human challenge model, male and female volunteers were investigated in a randomized, placebo-controlled, double-blind study. Four subjects received a single oral dose of 600 mg (base) tafenoquine, and 2 subjects received matching placebo, 1 day prior to challenge with mosquitoes infected with *P. falciparum*. Three of the 4 subjects who received tafenoquine were protected, while the fourth subject developed oligosymptomatic malaria on day 31, with drug concentrations one-half of those observed in the protected subjects. Both subjects randomized to placebo developed symptomatic parasitemia on day 10 (25).

In a randomized, double-blind study, the efficacy and safety of tafenoquine were investigated in the chemoprophylaxis of malaria in Gabon, an area endemic for *P. falciparum*. A total of 410 subjects completed both an initial curative regimen of halofantrine followed by a prophylaxis regimen of tafenoquine (250, 125, 62.5 or 31.25 mg) or placebo for 3 days. The primary and secondary endpoints were the number of individuals with positive blood smears by days 56 and 77, respectively. By day 56, 4 positive blood smears in each of the placebo and tafenoquine 31.25 mg groups had been recorded. By day 77, there were 34 positive blood smears, 30 of which were in the placebo or lowest dose tafenoquine group. None were recorded in the tafenoquine 250 mg group. The most frequently observed adverse events were headache, abdominal pain and fever, but the numbers of adverse events did not differ significantly between the treatment groups (26).

Tafenoquine was also investigated for prophylaxis against *P. falciparum* in a double-blind, placebo-controlled, randomized clinical trial in western Kenya. A total of 235 volunteers received halofantrine 250 mg per day for 3 days, to clear existing parasites, followed by a loading dose of tafenoquine (or matching placebo). Volunteers were randomized to receive 1 of 4 regimens: loading doses of 400, 200 or 400 mg tafenoquine for 3 days followed by placebo, 200 or 400 mg tafenoquine weekly, respectively, or placebo throughout. Prophylaxis continued for up to 13 weeks. Protective efficacies of evaluable subjects in the 3 active treatment groups compared with placebo were 68%, 86% and 89%, respectively, indicating that the prophylactic regimens of tafenoquine taken for up to 13 weeks were highly efficacious. Similar numbers of volunteers in the 4 treatment groups reported adverse events; dermatological events were more common in the tafenoquine groups than in the placebo group and gastrointestinal upset was more common in the tafenoquine 400 mg weekly group (27).

In a further randomized, double-blind, placebo-controlled, dose-ranging study, tafenoquine and mefloquine were investigated for weekly prophylaxis against *P. falciparum* in northern Ghana. Following a radical cure regimen to eliminate active and latent Plasmodium parasites, subjects were assigned to one of 6 prophylaxis regimens: tafenoquine 25, 50, 100 or 200 mg, mefloquine 250 mg, or placebo. Subjects received a loading dose for 3 days, followed by weekly doses for up to 12 weeks. Protective efficacies relative to placebo were 32%, 84%, 87% and 86% for the 25, 50, 100 and 200 mg tafenoquine groups and 86% for the mefloquine group. Adverse event rates in the tafenoquine group were comparable to those observed in the placebo group and showed no evidence of a dose-related effect. Of the 9 serious adverse events reported during the study, none were considered by study physicians to be related to the study drug (28).

A total of 654 volunteers were recruited into a double-blind, comparative trial of tafenoquine and mefloquine for the prophylaxis of malaria in nonimmune Australian soldiers in East Timor. Subjects received weekly dosing for 6 months and were followed up for a further 6 months. No subjects developed malaria during the prophylaxis phase. Drug-related adverse events were reported by 13.4% subjects in the tafenoquine group and 11.7% subjects in the mefloquine group during this phase (29).

The effectiveness, safety and tolerability of primaquine and tafenoquine were compared in an open-label, randomized study of the postexposure prophylaxis of *P. vivax* malaria in Australian Defence Force personnel returning from Papua New Guinea. A total of 586 personnel received one of 3 prophylaxis regimens: primaquine 22.5 mg (base) daily for 14 days (n=214), tafenoquine 400 mg (base) daily for 3 days (n=292) or tafenoquine 200 mg (base) b.i.d. for 3 days. Within 12 months, 6 of the subjects who received primaquine and 7 of the 378 subjects who received tafenoquine had developed *P. vivax* malaria. The onset of infections tended to be later following tafenoquine administration. Adverse events were more frequently reported in the tafenoquine groups, but were generally mild and transient in nature. The authors concluded that tafenoquine was no more effective than primaquine in preventing *P. vivax* malaria in this group of subjects (30).

In a randomized, dose-ranging study tafenoquine was shown to be safe, well tolerated and effective in preventing *P. vivax* relapse. Forty-four *P. vivax*-infected patients were randomly assigned to 1 of 4 treatment regimens: 3 groups received a blood schizontocidal dose of chloroquine followed by tafenoquine (300 mg for 7 days [A], 500 mg for 3 days, repeated 1 week after the initial dose [B], or a single dose of 500 mg [C]) and the fourth group received chloroquine only. In patients who completed at least 2 months of follow-up, there was 1 relapse in each of groups B and C, compared with 4 in the chloroquine only group. Mild, transient headache, loose stools and diarrhea, nausea and abdominal discomfort occurred in a minority of patients in all treatment groups (31).

Tafenoquine is likely to exert a hemolytic action in individuals who are glucose-6-phosphate dehydrogenase (G6PD) deficient. This effect is associated with administration of 8-aminoquinolines and is a side effect observed with primaquine. It can lead to hemolytic anemia in susceptible individuals (6). These individuals have been excluded from clinical studies for this reason, but in one study, 2 hemolytic events occurred in volunteers who

Table I: Clinical studies of tafenoquine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy Volunteers	Randomized, double-blind	Tafenoquine, 4, 8, 16, 36, 72, 100, 144, 192, 240, 250, 288, 300, 350, 400, 500, or 600 mg [escalated dose] po sd (n=3 in each dose range) (n=48) Placebo (n=2 in each dose range) (n=32)	80	Tafenoquine produced greater erythrocytic accumulation with a longer half-life in healthy male volunteers and could be effectively used both as weekly prophylaxis and short-term regimen in treating patients with malaria	23
Malaria prophylaxis	Open	Tafenoquine, 600 mg od x 2 d [before sporozoite challenge] → 300 mg 1x/wk x 4 wk (n=10) Placebo (n=2)	12	Subjects who received tafenoquine either showed asymptomatic parasitemia or remained aparasitemic, while those treated with placebo developed symptomatic parasitemia. Tafenoquine was well tolerated, with only mild adverse events reported	24
Malaria prophylaxis	Randomized, open	Tafenoquine, 31.25 mg od x 3 d (n=81) Tafenoquine, 62.5 mg od x 3 d (n=86) Tafenoquine, 125 mg od x 3 d (n=83) Tafenoquine, 250 mg od x 3 d (n=84) Placebo (n=84)	426	After 77 days of follow-up, etaquine at doses higher than 31.25 mg provided significant protection against malaria infection compared to placebo. Most adverse events associated with tafenoquine were mild and self-limiting and no significant differences were found between safety profiles of the placebo and active drug groups	26
Malaria prophylaxis	Randomized, double-blind	Tafenoquine, 400 mg od x 3 d (n=60) Tafenoquine, 200 mg od x 3 d → 200 mg 1x/wk x 13 wk (n=55) Tafenoquine, 400 mg od x 3 d → 400 mg 1x/wk x 13 wk (n=59) Placebo (n=61)	249	Tafenoquine administered for 13 weeks was well tolerated and effective in the prevention of malaria	27
Malaria	Randomized, double-blind	Radical cure regimen x 18 d → Tafenoquine, 25 mg od x 3 d → 25 mg 1x/wk x 12 wk (n=93) Radical cure regimen x 18 d → Tafenoquine, 50 mg od x 3 d → 50 mg 1x/wk x 12 wk (n=93) Radical cure regimen x 18 d → Tafenoquine, 100 mg od x 3 d → 100 mg 1x/wk x 12 wk (n=94) Radical cure regimen x 18 d → Tafenoquine, 200 mg od x 3 d → 200 mg 1x/wk x 12 wk (n=93) Radical cure regimen x 18 d → Mefloquine, 250 mg od x 3 d → 250 mg 1x/wk x 12 wk (n=46) Radical cure regimen x 18 d → Placebo (n=94)	530	All four tafenoquine doses were as effective as mefloquine in providing protection against malaria reinfection. Tafenoquine was well tolerated, and when administered at doses of 50, 100 or 200 mg it was better than placebo in increasing the percentage of patients who remained uninfected after 12 weeks. No serious adverse events were associated with the drug	28
Malaria prophylaxis	Randomized, double-blind	Tafenoquine/Placebo group 1x/wk x 6 mo → follow-up x 6 mo Mefloquine/Primaquine 1x/wk x 6 mo → follow-up x 6 mo	654	Tafenoquine and mefloquine were well tolerated and no subjects developed malaria during the prophylaxis phase with both drugs	29
Malaria prophylaxis	Open	Tafenoquine, 200 mg bid x 3 d (n=86) Tafenoquine, 400 mg od x 3 d (n=292) Primaquine, 22.5 mg od x 14 d (n=214)	586	Both tafenoquine and primaquine were well tolerated and effective in the prevention of malaria, although tafenoquine was associated with a slightly higher incidence of gastrointestinal events	30
Malaria	Randomized, open	Tafenoquine, 300 mg od x 7 d (n=15) Tafenoquine, 500 mg od x 3 d ® 500 mg od x 3 d [1 week after the first dose] (n=11) Tafenoquine, 500 mg sd (n=9)$ No treatment (n=9)	44	Tafenoquine reduced the incidence of relapse compared with chloroquine alone after a follow-up period of 2-6 mo in patients with malaria. Tafenoquine was also well tolerated and no patients withdrew from the study due to adverse events	31

received tafenoquine 400 mg daily for 3 days and whose G6PD status had been incorrectly determined during screening procedures (27). The 8-aminoquinoline antimalarials can also produce high, dose-related levels of methemoglobin (MHb), which can be a dose-limiting side effect. However, this can also be the intended therapeutic effect of one class of drugs used to treat cyanide poisoning. A pharmacokinetic-pharmacodynamic model has been developed to predict MHb levels after tafenoquine administration in beagle dogs (22). Mean plateau MHb levels of 2.5% and 4.5% in subjects who received 200 mg and 400 mg tafenoquine weekly have been observed, but these concentrations were not considered to be of clinical concern (27).

In summary, tafenoquine is an effective and well tolerated antimalarial, both for chemoprophylaxis against *P. falciparum* and also as treatment against latent liver forms of *P. vivax*. Recognized side effects of the 8-aminoquinoline class of drugs may limit its use in certain populations; however, it has the advantage over primaquine that it can be administered weekly because of its longer elimination half-life. Tafenoquine is in phase III trials and filing is anticipated in 2005.

Source

Walter Reed Army Institute of Research, Washington, DC (US); licensed to GlaxoSmithKline plc (GB).

References

1. Ugwuegbulam, C.O., Foy, J.E. (GlaxoSmithKline plc; GlaxoSmithKline Inc.). *Process for the preparation of anti-malarial drugs.* US 6479660, WO 9713753.

2. Blumbergs, P., LaMontagne, M.P. (Department of the Army). *4-Methyl-5-(unsubstd. and substd. phenoxy)-2,6-dimethoxy-8-(aminoalkylamino)quinolines.* US 4617394.

3. LaMontagne, M.P., Blumbergs, P., Smith, D.C. *Antimalarials. 16. Synthesis of 2-substituted analogues of 8-[(4-amino-1-methylbutyl)amino]-6-methoxy-4-methyl-5-[3-(trifluoromethyl)-phenoxy]quinoline as candidate antimalarials.* J Med Chem 1989, 32: 1728-32.

4. Strube, R.E., LaMontagne, M.P. *(Department of the Army). 4-Methyl-5-(unsubstd. and substd. phenoxy)-6-methoxy-8-(aminoalkylamino)quinolines.* US 4431807.

5. LaMontagne, M.P., Blumbergs, P., Strube, R.E. *Antimalarials. 14. 5-(Aryloxy)-4-methylprimaquine analogues. A highly effective series of blood and tissue schizonticidal agents.* J Med Chem 1982, 25: 1094-7.

6. Peters, W. *The evolution of tafenoquine - antimalarial for a new millennium?* J Roy Soc Med 1999, 92: 345-52.

7. Edstein, M.D., Kocisko, D.A., Brewer, T.G., Walsh, D.S., Eamsila, C., Charles, B.G. *Population pharmacokinetics of the new antimalarial agent tafenoquine in Thai soldiers.* Br J Clin Pharmacol 2001, 52: 663-70.

8. Coleman RE. *Sporontocidal activity of the antimalarial WR-238605 against Plasmodium berghei ANKA in Anopheles stephensi.* Am J Trop Med Hyg 1990, 42: 196-205.

9. Coleman, R.E., Clavin, A.M., Milhous, W.K. *Gametocytocidal and sporontocidal activity of antimalarials against Plasmodium berghei ANKA in ICR mice and Anopheles stephensi mosquitoes.* Am J Trop Med Hyg 1992, 46: 169-82.

10. Coleman, R.E., Nath, A.K., Schneider, I., Song, G.H., Klein, T.A., Milhous, W.K. *Prevention of sporogony of Plasmodium falciparum and P. berghei in Anopheles stephensi mosquitoes by transmission blocking antimalarials.* Am J Trop Med Hyg 1994, 50: 646-53.

11. Peters, W., Robinson, B.L., Milhous, W.K. *The chemotherapy of rodent malaria. LI. Studies on a new 8-aminoquinoline, WR 238,605.* Ann Trop Med Parasitol 1993, 87: 547-52.

12. Cooper, R.D., Milhous, W.K., Rieckmann, K.H. *The efficacy of WR238605 against the blood stages of a chloroquine resistant strain of Plasmodium vivax.* Trans R Soc Trop Med Hyg 1994 88: 691-2.

13. Obaldia, N. III, Rossan, R.N., Cooper, R.D., Kyle, D.E., Nuzum, E.O., Rieckmann, K.H., Shanks, G.D. *WR 238605, chloroquine, and their combinations as blood schizonticides against a chloroquine-resistant strain of Plasmodium vivax in Aotus monkeys.* Am J Trop Med Hyg 1997, 56: 508-10.

14. Puri, S.K., Dutta, G.P. *Blood schizontocidal activity of WR 238605 (tafenoquine) against Plasmodium cynomolgi and Plasmodium fragile infections in rhesus monkeys.* Acta Trop 2003, 86: 35-40.

15. Puri, S.K., Dutta, G.P., Kamboj, V.P., Nuzum, E.O., Kyle, D.E., Brueckner, R.P., Horton, R.J., Schuster, B.G., Milhous, W.K. *Combination radical curative activity of WR238605 plus halofantrine in the P. cynomolgi rhesus monkey relapsing malaria model.* Am J Trop Med Hyg 1996, 55(2, Suppl.): Abst 4.

16. Kyle, D.E., Bruckner, R.P., Gettayacamin, M., Milhous, W.K. *Anti-erythrocytic stage activity of WR238605 (racemate), its isomers, and putative metabolites in vitro and in vivo.* Am J Trop Med Hyg 1997, 57(3, Suppl.): Abst 521.

17. Queener, S.F., Bartlett, M.S., Nasr, M., Smith, J.W. *8-Aminoquinolines effective against Pneumocystis carinii in vitro and in vivo.* Antimicrob Agents Chemother 1993, 37: 2166-72.

18. Bartlett, M.S., Queener, S.F., Tidwell, R.R., Milhous, W.K., Berman, J.D., Ellis, W.Y., Smith, J.W. *8-Aminoquinolines from Walter Reed Army Institute for Research for treatment and prophylaxis of Pneumocystis pneumonia in rat models.* Antimicrob Agents Chemother 1991, 35: 277-82.

19. Queener, S.F., Dean, R.A., Bartlett, M.S., Milhous, W.K., Berman, J.D., Ellis, W.Y., Smith, J.W. *Efficacy of intermittent dosage of 8-aminoquinolines for therapy or prophylaxis of Pneumocystis pneumonia in rats.* J Infect Dis 1992, 165: 764-8.

20. Marley, S.E., Eberhard, M.L., Steurer, F.J., Ellis, W.L., McGreevy, P.B., Ruebush, T.K. II. *Evaluation of selected antiprotozoal drugs in the Babesia microti-hamster model.* Antimicrob Agents Chemother 1997, 41: 91-4.

21. Theoharides, A.D., Smyth, M., Anders, J., Chung, H. *Pharmacokinetics of a new primaquine analog in the rat.* Fed Proc 1985, 44(4): Abst 4150.

22. Brueckner, R.P., Fleckenstein, L. *Simultaneous modeling of the pharmacokinetics and methemoglobin pharmacodynamics of an 8-aminoquinoline candidate antimalarial (WR 238605).* Pharm Res 1991, 8: 1505-10.

23. Brueckner, R.P., Lasseter, K.C., Lin, E.T., Schuster, B.G. *First-time-in-humans safety and pharmacokinetics of WR 238605, a new antimalarial.* Am J Trop Med Hyg 1998, 58: 645-9.

24. Brueckner, R., Coster, T., Kin-Ahn, G., Shmuklarsky, M., Kyle, D., Wesche, D., Kain, K., Page, N., Schuster, B. *Safety, pharmacokinetics and antimalarial activity of WR 238605 in man.* Am J Trop Med Hyg 1997, 57(3, Suppl.): Abst 522.

25. Brueckner, R.P., Coster, T., Wesche, D.L., Shmuklarsky, M., Schuster, B.G. *Prophylaxis of Plasmodium falciparum infection in a human challenge model with WR 238605, a new 8-aminoquinoline antimalarial.* Antimicrob Agents Chemother 1998, 42: 1293-4.

26. Lell, B., Faucher, J.-F., Missinou, M.A., Borrmann, S., Dangelmaier, O., Horton, J., Kremsner, P.G. *Malaria chemoprophylaxis with tafenoquine: A randomised study.* Lancet 2000, 355: 2041-5.

27. Shanks, G.D., Oloo, A.J., Aleman, G.M., Ohrt, C., Klotz, F.W., Braitman, D., Horton, J., Brueckner, R. *A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against Plasmodium falciparum malaria.* Clin Infect Dis 2001, 33: 1968-74.

28. Hale, B.R., Owusu-Agyei, S., Fryauff, D.J. et al. *A randomized, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against Plasmodium falciparum.* Clin Infect Dis 2003, 36: 541-9.

29. Nasveld, P., Brennan, L., Edstein, M., Kitchener, S., Leggat, P., Rieckmann, K. *A randomised, double-blind comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers.* 51st Annu Meet Am Soc Trop Med Hyg (Nov 10-14, Denver) 2002, Abst 326.

30. Nasveld, P., Kitchener, S., Edstein, M., Rieckmann, K. *Comparison of tafenoquine (WR238605) and primaquine in the post exposure (terminal) prophylaxis of vivax malaria in Australian Defence Force personnel.* Trans R Soc Trop Med Hyg 2002, 96: 683-4.

31. Walsh, D.S., Looareesuwan, S., Wilairatana, P. et al. *Randomized dose-ranging study of the safety and efficacy of WR 238605 (tafenoquine) in the prevention of relapse of Plasmodium vivax malaria in Thailand.* J Infect Dis 1999, 180: 1282-7.

Additional References

Anders, J.C., Chung, H., Theoharides, A.D. *Methemoglobin formation resulting from administration of candidate 8-aminoquinoline antiparasitic drugs in the dog.* Fundam Appl Toxicol 1988, 10: 270-5.

Fisk, T.L., Millet, P., Collins, W.E., Nguyen-Dinh, P. *In vitro activity of antimalarial compounds on the exoerythrocytic stages of Plasmodium cynomolgi and P. knowlesi.* Am J Trop Med Hyg 1989, 40: 235-9.

Smith, J.W., Queener, S.F., Durkin, M.M., Bartlett, M.S. *Prophylaxis of Pneumocystis carinii (PC) pneumonia in rats with 8-aminoquinolines.* 30th Intersci Conf Antimicrob Agents Chemother (Oct 21-24, Atlanta) 1990, Abst 860.

Brueckner, R.P., Fleckenstein, L. *Combined pharmacokinetic-pharmacodynamic (PK-PD) model to predict methemoglobin formation by a new candidate antimalarial.* Clin Pharmacol Ther 1990, 47(2): Abst PII-35.

Steinhaus, R.K., Baskin, S.I., Clark, J.H., Kirby, S.D. *Formation of methemoglobin and metmyoglobin using 8-aminoquinoline derivatives or sodium nitrite and subsequent reaction with cyanide.* J Appl Toxicol 1990, 10: 345-51.

Milhous, W.K., Breuckner, R.P., Theoharides, A.D., Schuster, B. *Preclinical efficacy of WR238605.* 31st Intersci Conf Antimicrob Agents Chemother (Sept 29-Oct 2, Chicago) 1991, Abst 376.

Nuzum, E.O., Gerena, L., Kyle, D.E., Milhous, W.K. *The in vitro activity of 8-aminoquinolines and their potential for the treatment of multidrug-resistant malaria.* Am J Trop Med Hyg 1992, 47(4, Suppl.): Abst 208.

Scharf, B.A., Fricke, R.F., Baskin, S.I. *Comparison of methemoglobin formers in protection against the toxic effects of cyanide.* Gen Pharmacol 1992, 23: 19-25.

Ittarat, I., Webster, H.K., Yuthavong, Y. *High-performance liquid chromatographic determination of dihydroorotate dehydrogenase of Plasmodium falciparum and effects of antimalarials on enzyme activity.* J Chromatogr - Biomed Appl 1992, 582: 57-64.

Goheen, M.P., Bartlett, M.S., Shaw, M.M., Queener, S.F., Smith, J.W. *Effects of 8-aminoquinolines on the ultrastructural morphology of Pneumocystis carinii.* Int J Exp Pathol 1993, 74: 379-87.

Ittarat, I., Asawamahasakda, W., Meshnick, S.R. *The effects of antimalarials on the Plasmodium falciparum dihydroorotate dehydrogenase.* Exp Parasitol 1994, 79: 50-6.

Idowu, O.R., Peggins, J.O., Brewer, T.G., Kelley, C. *Metabolism of a candidate 8-aminoquinoline antimalarial agent, WR 238605, by rat liver microsomes.* Drug Metab Dispos 1995, 23: 1-17.

Karle, J.M., Olmeda, R., Freeman, S.G., Schroeder, A.C. *Quantification of the individual enantiomer plasma concentrations of the candidate antimalarial agent N^4-[2,6-dimethoxy-4-methyl-5-[(3-trifluoromethyl)phenoxy]-8-quinolinyl]-1,4-pentanediamine (WR 238,605).* J Chromatogr B - Biomed Appl 1995, 670: 251-7.

Kain, K.C. *Malaria chemoprophylaxis.* 14th Int Congr Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst A-17-3.

Kinnamon, K.E., Poon, B.T., Hanson, W.L., Waits, V.B. *Primaquine analogues that are potent anti-Trypanosoma cruzi agents in a mouse model.* Ann Trop Med Hyg 1996, 90: 467-74.

Fleck, S.L., Robinson, B.L., Peters, W. T*he chemotherapy of rodent malaria. LIV. Combinations of "Fenozan B07" (Fenozan-50F), a difluorinated 3,3'-spirocyclopentane 1,2,4-trioxane, with other drugs against drug-sensitive and drug-resistant parasites.* Ann Trop Med Parasitol 1997, 91: 33-9.

Shanks, G.D., Oloo, A., Klotz, F.W., Aleman, G.M., Wesche, D., Brueckner, R., Horton, J. *Evaluation of weekly etaquine (WR238605) compared to placebo for chemosuppression of Plasmodium falciparum in adult volunteers in western Kenya.* Am J Trop Med Hyg 1997, 57(3, Suppl.): Abst 518.

Walsh, D.S., Looareesuwan, S., Wilairatana, P., Heppner, D.G., Brewer, T.G., Kyle, D.E., Milhous, W.K., Schuster, B.G., Horton, J., Brueckner, R.P. *Dose-ranging study of the safety and efficacy of WR 238605 in the prevention of relapse of Plasmodium vivax infection in Thailand.* Am J Trop Med Hyg 1997, 57(3, Suppl.): Abst 523.

Ball, M.D., Meshnick, S.R., Milhous, W.K., Ellis, W.Y., Shaw, M.M., Smith, J.W., Bartlett, M.S. *Activity of 8-aminoquinolines and their metabolites against Pneumocystis carinii of rat origin.* 98th Gen Meet Am Soc Microbiol (May 17-21, Atlanta) 1998, Abst F-106.

Sauerwein, R. *Transmission blocking drugs or vaccines for control of malaria.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst TuS4.

Kocisko, D.A., Walsh, D.S., Eamsila, C., Edstein, M.D. *Measurement of tafenoquine (WR 238605) in human plasma and venous and capillary blood by high-pressure liquid chromatography.* Ther Drug Monit 2000, 22: 184-9.

Hale, B.R., Owusu-Agyei, S., Koram, K.A. et al. *A randomized, double-blinded, placebo-controlled trial of tafenoquine for prophylaxis against Plasmodium falciparum in Ghana.* Am J Trop Med Hyg 2000, 62(3, Suppl.): Abst 18.

Nasveld, P.E., Edstein, M.D., Kitchener, S.J., Rieckmann, K.H. *Comparison of tafenoquine (WR238605) and primaquine in the terminal prophylaxis of vivax malaria in Australian Defence Force personnel serving in Bougainville, Papua New Guinea.* Am J Trop Med Hyg 2000, 62(3, Suppl.): Abst 424.

Cummings, J.F., Stoute, J.A., Heppner, D.G. et al. *A critical evaluation of exclusion/inclusion criteria for a randomized, double-blind, placebo controlled evaluation of weekly tafenoquine (WR 238605/SB 252263) compared to mefloquine for chemosuppression of Plasmodium falciparum in Western Kenya.* Am J Trop Med Hyg 2000, 62(3, Suppl.): Abst 438.

Ramharter, M., Noedl, H., Thimasarn, K., Wiedermann, G., Wernsdorfer, G., Wernsdorfer, W.H. *In vitro activity of tafenoquine alone and in combination with artemisinin against Plasmodium falciparum.* Am J Trop Med Hyg 2002, 67: 39-43.

Gerena, L., Kyle, D.E. *Synergy of tafenoquine and methylene blue versus Plasmodium falciparum in vitro.* 51st Annu Meet Am Soc Trop Med Hyg (Nov 10-14, Denver) 2002, Abst 466.

Jenwithisuk, R., Russell, B.M., Coleman, R.E., Sattabongkot, J. *The effect of antimalarials on the early exoerythrocytic development of Plasmodium falciparum and Plasmodium vivax in vitro.* 51st Annu Meet Am Soc Trop Med Hyg (Nov 10-14, Denver) 2002, Abst 469.