Drugs of the Future 2003, 28(3): 243-255

CCC: 0377-8282/2003

Review Article

Current trends in antimalarial chemotherapy

Arun Kumar, Sanjay Babu Katiyar, Anu Agarwal and Prem M.S. Chauhan*

*Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow, 226001, India. *Correspondence and present address: School of Chemical Sciences, University of East Anglia, Norwich, NR4 7TJ, U.K.*

CONTENTS

Abstract

This review discusses the commercially available antimalarial drugs that are classified according to their chemical entities and include quinolines, pyrimidines, amidines, guanidines, sulfonamides, sulfones, acridines, antibiotics and sesquiterpene lactones. New antimalarials reported during 2000 to June 2002 are also classified according to their chemical structures and include trioxanes, tetraoxane derivatives, other peroxides, quinolines and bisquinolines, isoquinolines, pyrimidines, acridine and bisacridine derivatives, bis acyl amino benzophenone, cinnamic acid derivatives, natural products, phenyl β-methoxy acrylates, pyrrolidines, carbolines, imidazoles and tropolones. The complications of malarial chemotherapy are also discussed.

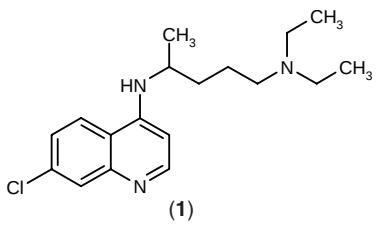
Introduction

Malaria is one of the major problems of many tropical and subtropical countries in the world. It is estimated that with 40% of the world's population exposed to the threat of malaria, there are an estimated 200 million clinical cases per year and 2 million deaths (1-3). Malaria is caused by protozoan parasites, namely *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodiun malariae* and *Plasmodium ovale*, and is transmitted to humans by female mosquitoes belonging to the genus Anopheles. Endemic maps indicate that *P. falciparum* and *P. vivax* account for 95% of malaria infections (4). Of these 2 types of infection, *P. falciparum* malaria does not cause relapse, has no periodicity and is associated with mortality while *P. vivax* malaria leads to relapse of the disease, has periodicity and causes morbidity (5, 6).

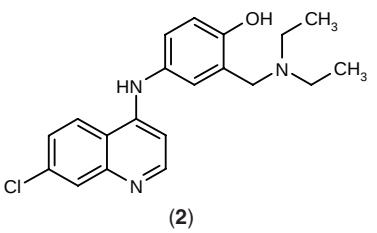
Available drugs for the management of malaria

Aminoquinolines

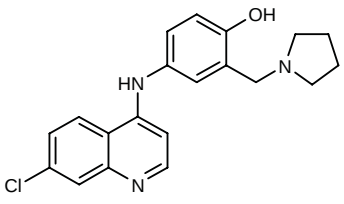
A number of blood schizontocidal drugs namely chloroquine (**1**), amodiaquine (**2**), amopyroquine (**3**), cycloquine (**4**) and mefloquine (**5**) belong to the 4-aminoquinoline group of antimalarials (1, 7-9). These drugs are ineffective for relapsing malaria. The 2 known 8-aminoquinoline compounds which are effective as antirelapse antimalarials are primaquine (**6**) and quinocide (**7**). These drugs are effective as gametocytocidal agents against all



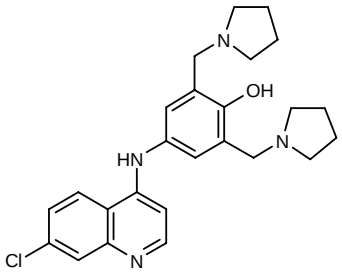
(**1**)

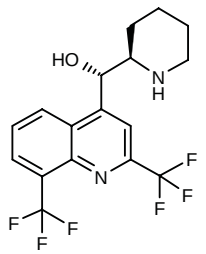


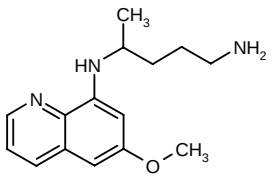
(**2**)

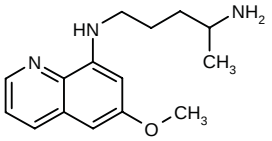


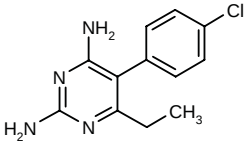
(**3**)

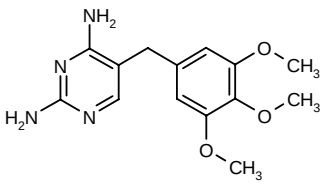

(**4**)

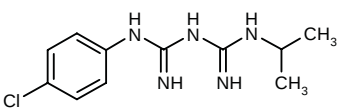

(**5**)

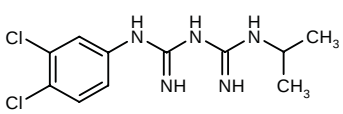

(**6**)

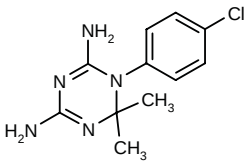

(**7**)

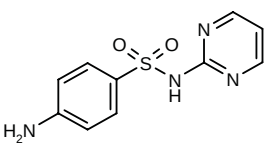

(**8**)

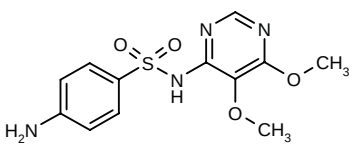

(**9**)

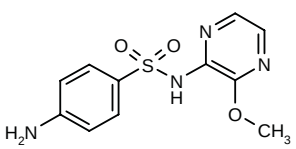

(**10**)


(**11**)


(**12**)


(**13**)


(**14**)


(**15**)

species of human malarial parasites and are also active against the primary exoerythrocytic stages of *P. vivax* and *P. falciparum* (1, 7-9).

Pyrimidines

Included in this class of drugs are compounds such as pyrimethamine (**8**) and trimethoprim (**9**), which are active against asexual blood stages of all types of malaria and also active against primary exoerythrocytic stages (1, 7-9).

Amidines and guanidines

Proguanil (**10**), chlorproguanil (**11**) and cycloguanil (**12**) are effective against the primary exoerythrocytic forms of *P. falciparum* and asexual blood forms of human malarial parasite (1, 7-9).

Sulfonamides and sulfones

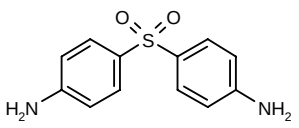
This class of drugs includes sulfadiazine (**13**), sulfadoxine (**14**), sulfalene (**15**), dapsone (**16**) and acedapsone (**17**) and are also effective against the asexual blood forms of *P. falciparum* (1, 7-9).

9-Aminoacridines

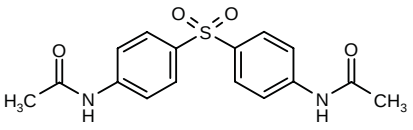
Mepacrine (**18**) is the only drug of this class and its action is similar to drugs belonging to the 4-aminoquinoline group (1, 7-9).

Antibiotics

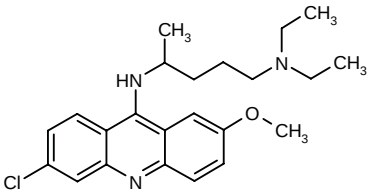
Several antibiotics such as tetracycline (**19**), doxycycline (**20**) and minocycline (**21**) are active against the primary exoerythrocytic and asexual blood stages of *P. falciparum* (1, 7-9).



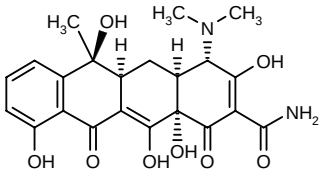
(**16**)



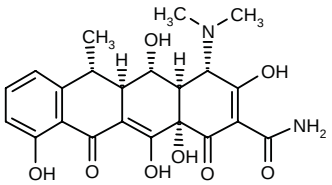
(**17**)



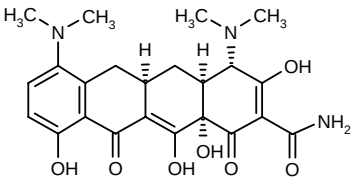
(**18**)



(**19**)



(**20**)



(**21**)

Sesquiterpene lactones

Artemisinin or qinghaosu (**22**) and its derivatives such as artemether (**23a**) and artesunate **(23b**) possess strong blood schizontocidal activity against *P. falciparum*. There is no evidence of activity against tissue stages (1, 7-9).

Recently available drugs

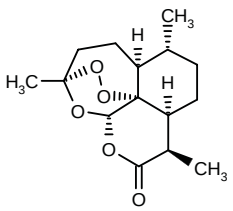
Two new 8-aminoquinolines are currently under clinical development. WR-238605 (**24a**) is reported to have higher activity, a longer half-life and less toxicity than primaquine. The other available compound, CDRI 80/53, (**24b**) is less toxic than primaquine (10). Jacobus pharmaceuticals is developing the dihydrofolate reductase (DHFR) inhibitor PS-15 (**24c**) for the potential treatment of *Toxoplasma gondii* and *Plasmodium* infection. It has shown activity against *Pneumocytis carinii* and *Mycobacterium avium* complex (MAC) (11).

New potential antimalarial agents

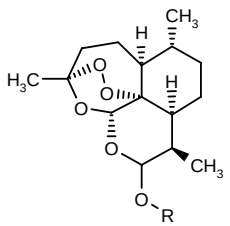
The new potential antimalarials are classified on the basis of their chemical entities.

Trioxanes

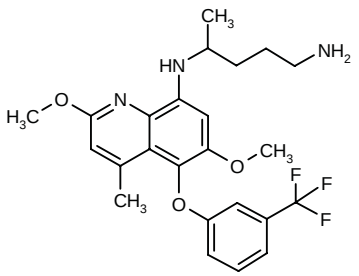
Several trioxane compounds showed good activity against multidrug-resistant *Plasmodium yoelii* in mice. Compound **25a,** the best of the series, was 2 times more active than arteether by the oral route (12). Fluorinated ether and ester analogues of artemether and arteether have been synthesized. The most active derivative **25b**



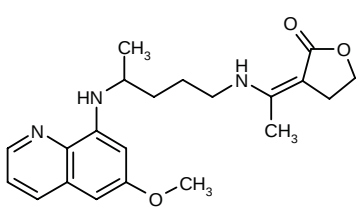
(**22**)



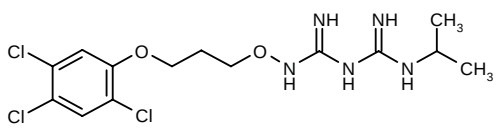
(**23a**) R = CH_3
(**23b**) R = $COCH_2CH_2COONa$



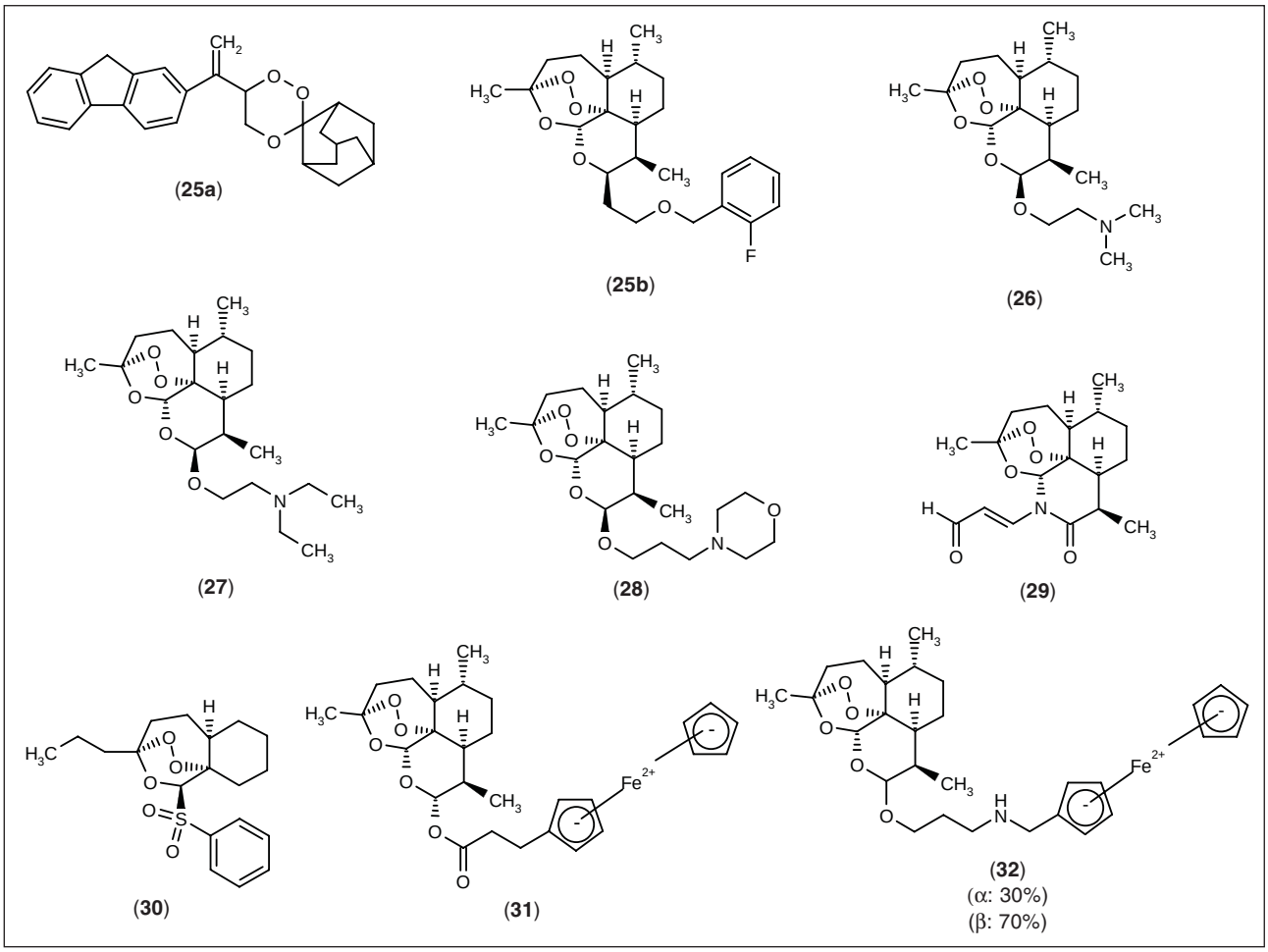
(**24a**)



(**24b**)



(**24c**)



was 15 times more potent than artemisinin against the HB3 strain of *P. falcifarum* (IC_{50} = 0.22 nM). *In vivo*, **25b** was again the most potent with an ED_{50} value of 5.08 mg/kg against *P. berghei* in a mouse model (13).

Artemisinin derivatives containing an amino group (β-isomer) were synthesized and tested in mice. Compounds **26, 27** and **28** were active against *P. berghei* by the oral route. The SD_{50} values for these compounds were 1.61, 1.74 and 1.82 mg/kg/day, respectively, and the SD_{90} values were 4.71, 5.08 and 5.28 mg/kg/day, respectively (14).

A series of *N*-substituted 11-azaartemisinins were prepared and tested against 2 drug-resistant strains of *P. falcifarum*. Compound **29** was most active with an IC_{50} value of 0.49 nM against both W2.18 and D6 strains (15).

A series of trioxanes featuring, sulfide, sulfone and sulfonamide substituents in diverse positions were prepared and tested for their antimalarial activity *in vitro*. The most active compound **30** had an IC_{50} value of 18 nM (16).

The 2 metallocenic derivatives **31** and **32** were found to be as potent as artemisinin *in vitro* (17). Compound **31** exhibited IC_{50} values of 10, 19 and 32 nM against malaria strains HB3, SGE2 and Dd2, respectively. IC_{50} values for compound **32** against these strains were 12, 11 and 14 nM, respectively.

C-10-Phenoxy derivatives of dihydroartemisinin were synthesized and tested as antimalarials *in vivo*. Compound **33** showed potent activity in a *P. berghei* and *P. yoelli* model. The ED_{50} and ED_{90} (mg/kg) values were 2.7 and 5.4 mg/kg, respectively, against *P. berghei* and 2.2 and 3.1 mg/kg, respectively, against *P. yoelli* (18).

3-Aryltrioxanes were synthesized and tested for their antimalarial activity *in vivo*. Compound **34** showed good activity in mice against *P. berghei* with ED_{50} and ED_{90} values of 4.0 and 8.0 mg/kg, respectively (19).

A series of C-10 carba-linked amino derivatives of dihydroartemisinin were prepared and screened for antimalarial activity *in vitro* and *in vivo*. Compound **35** showed the most potent activity *in vitro* (IC_{50} = 6.19 nM) and *in vivo* (ED_{50} = <10 mg/kg; ED_{90} = <10 mg/kg) (20).

Artemisinin derived trioxane dimers were synthesized and compounds **36** and **37** showed promise as chemotherapies for malaria *in vitro*, displaying IC_{50} values of 28 and 15 nM, respectively (21).

Tetraoxane derivatives

Tetraoxane 7,8,15,16-tetraoxadispiro[5.2.5.2]hexadecane **38** showed potent antimalarial activity *in vitro* against *P. berghei* with IC_{50} values of 38 and 26 nM against the D6 and W2 strains, respectively (22).

Cholic acid derived 1,2,4,5-tetraoxanes were synthesized and tested for antimalarial activity. Compound **39** was the most active with an IC_{50} value of 9.29 nM against the D6 clone (23).

From among the 1,2,4,5-tetraoxacycloalkanes that were synthesized, compound **40** showed considerable potential as a new antimalarial drug (24). The compound exhibited *in vitro* activity at a concentration of 2.5×10^{-8} M. ED_{50} values of 12 mg/kg i.p. and 20 mg/kg p.o. and ED_{90} values of 20 mg/kg i.p. and 40 mg/kg p.o. were obtained *in vivo*.

Other peroxides

The *tert*-butyl-peroxyamines were synthesized as antimalarials and evaluated for activity in vitro against *P. falciparum* and *in vivo* against *P. berghei* in mice. Compound **41** was found to have the most potent activity *in vivo* at doses of 80 and 160 mg/kg (25).

Several bis(alkyldioxy)alkanes and related acyclic peroxides were prepared and tested for antimalarial activity *in vitro* and *in vivo*. Compound **42** was found to have potent activity via both i.p. and p.o. routes. The ED_{50} and ED_{90} values for the compound were 13 and 20 mg/kg i.p., respectively, and 30 and 60 mg/kg p.o., respectively (26).

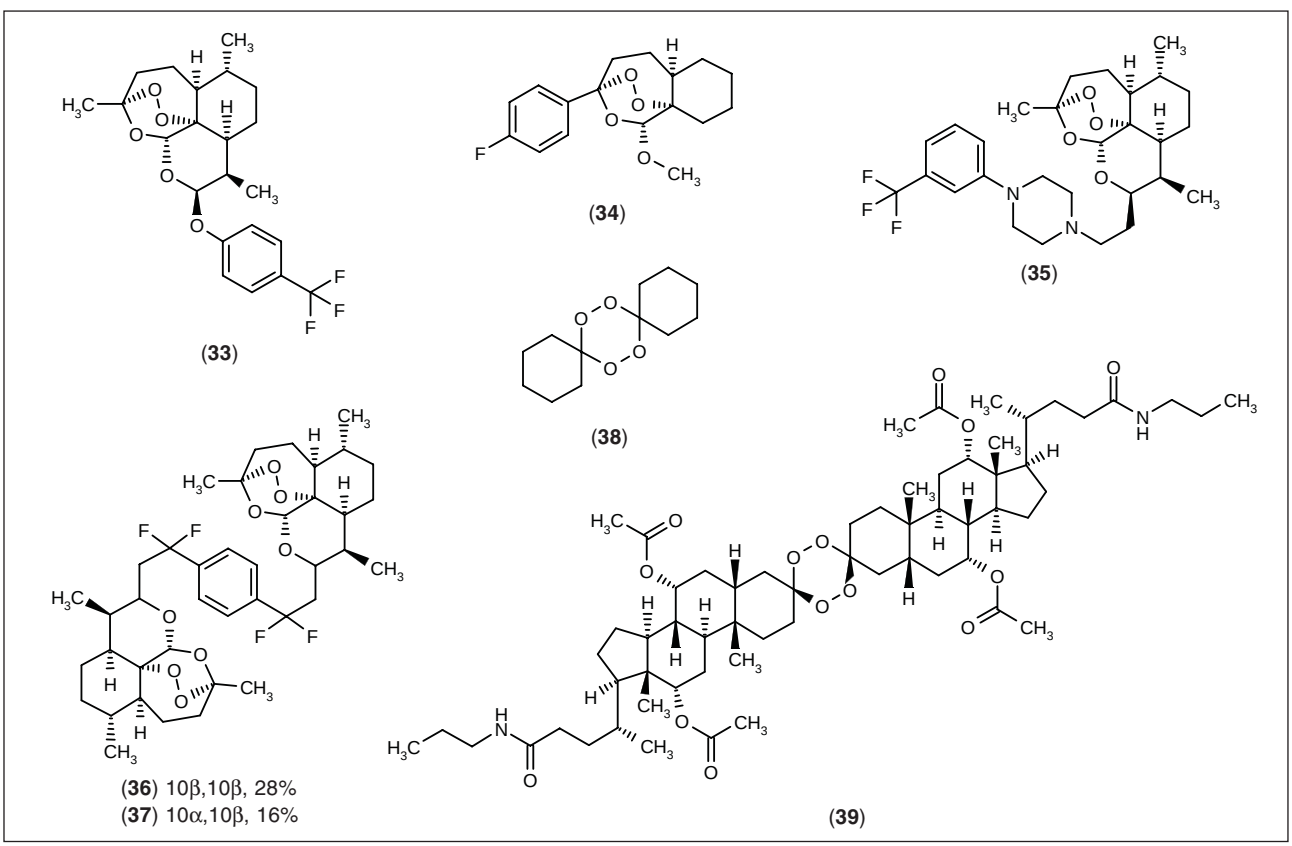
The 1,2-dioxane derivatives were synthesized and tested. Compound **43** was found to exhibit potent antimalarial activity with an IC_{50} value of 12 μM (27).

Quinolines and bisquinolines

A new series of 4-aminoquinolines with 2 proton accepting side chains has been synthesized and tested for antimalarial activity *in vivo* and *in vitro*. Compound **44** cured mice infected by *P. berghei*, reducing parasitemia by 100% at a dose of 40 mg/kg at day 4. The compound also exhibited *in vitro* activity with an IC_{50} value of 9.5 nM obtained (28).

A total of 13 *N*,*N*-bis(7-chloroquinolin-4-yl)alkanediamines were synthesized and screened against *P. falciparum in vitro* and *P. berghei in vivo*. Compound **45** was the most potent bisquinoline *in vitro* with IC_{50} values of 1 and 1.4 nM against the D6 and W2 strains, respectively. Cure rates of 80% and 100% were achieved *in vivo* at doses of 160 and 320 mg/kg, respectively (29).

Bisamides were synthesized from aliphatic diacids with 6-amino- and 8-amino-4-[4-(diethylamino)-1-methylbutylamino]quinoline and screened against chloroquine-sensitive and -resistant strains of *P. falciparum in vitro*.



(**33**)

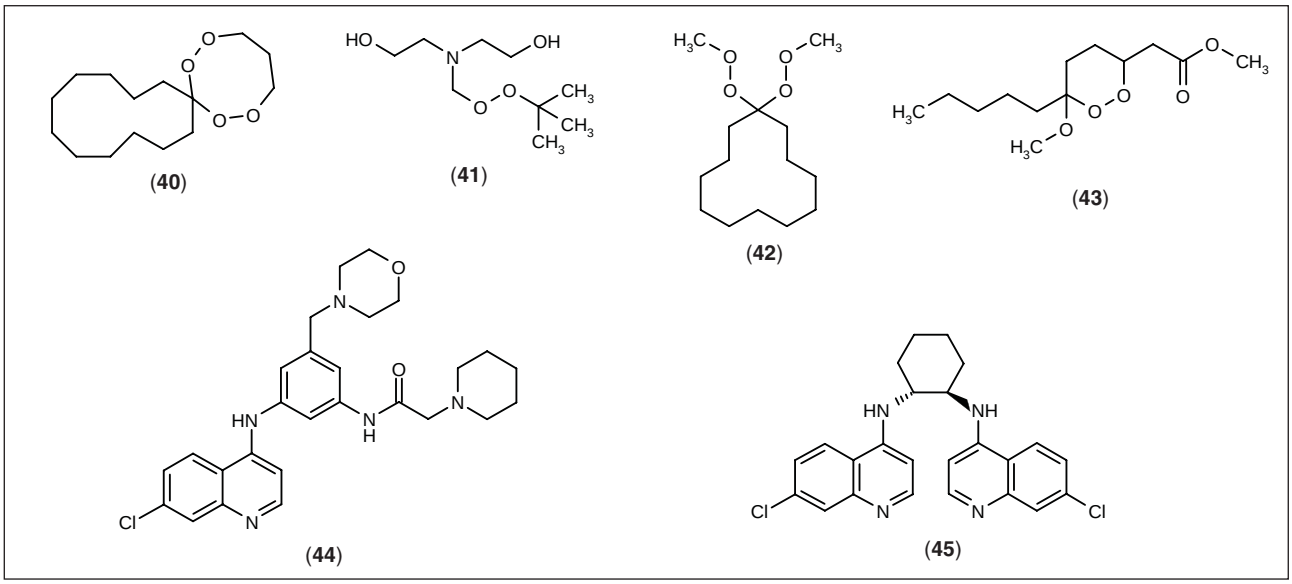
(**34**)

(**35**)

(**38**)

(**36**) 10β,10β, 28%
(**37**) 10α,10β, 16%

(**39**)

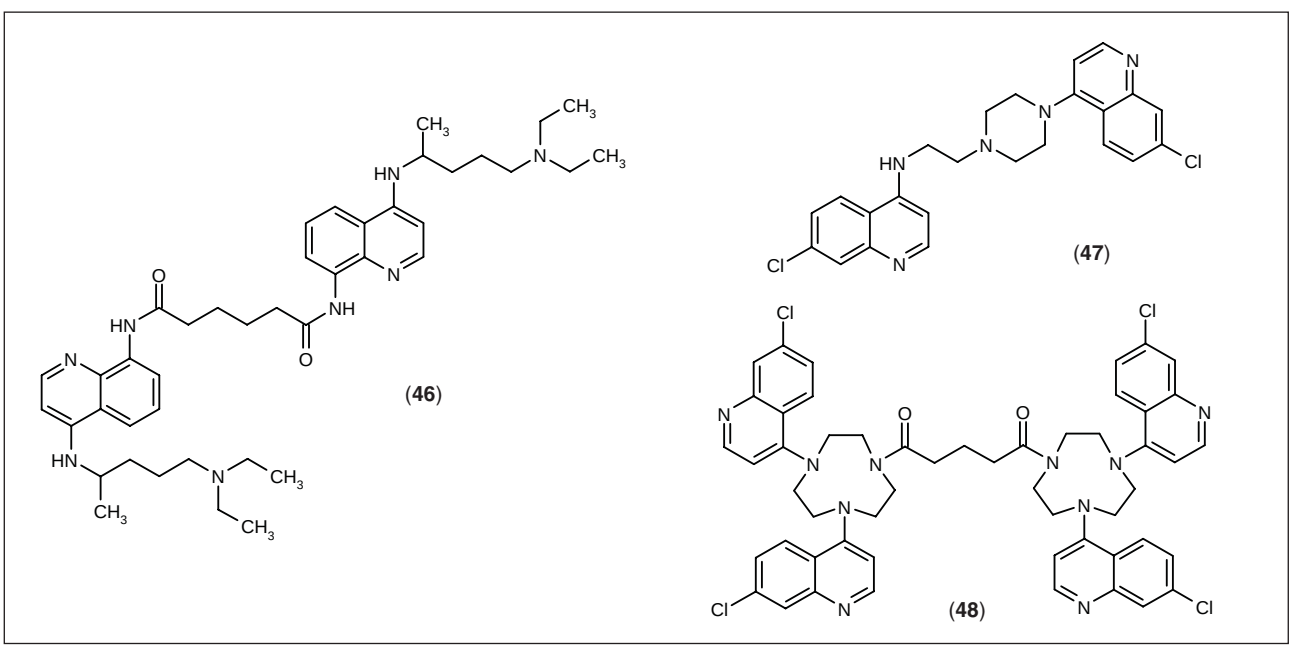


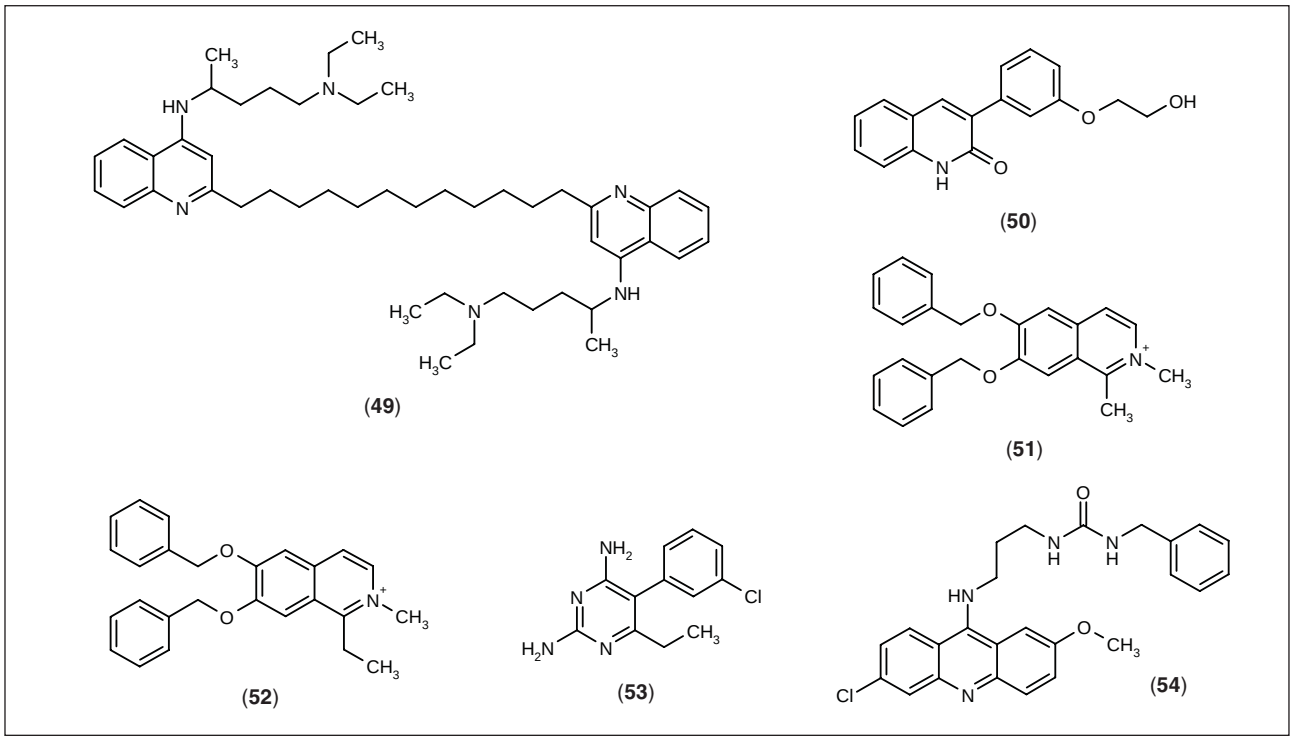
Compound **46** was the most active with an IC_{50} value of 0.13 μM (30).

N,N-Bis(7-chloroquinolin-4-yl)heteroalkanediamines were synthesized and screened against *P. falciparum in vitro* and *P. berghei in vivo*. The bisquinolines were potent inhibitors of hematin polymerization with IC_{50} values falling in the narrow range of 5-20 μM. The most active compound was **47**, which showed potent activity *in vitro*, displaying IC_{50} values of 1.2 and 9.0 nM for D6 and W2 strains, respectively) (31).

Bis-, tris- and tetraquinolines with linear or cyclic amino linkers were synthesized and tested as antimalarials *in vitro*. Compound **48** was found to have potent activity *in vitro* with an IC_{50} value of 29.2 nM obtained against the W2 strain and values of 18.3, 18.5 and 17.9 nM reported against fcB1R, D6 and F32 *P. falciparum* strains, respectively (32).

Novel bisquinoline compounds were synthesized comprising 4-[4-(diethylamino)-1-methylbutyl)amino]-quinoline units joined through the 2 position by a $(CH_2)n$ linker. Their ability to inhibit the growth of both chloroquine-sensitive (D10) and -resistant (K1) strains of *P. falciparum* were examined. The most active compound was **49** showing effects similar to chloroquine in 3 of the assays. However, **49** was even more active against the resistant strain (IC_{50} = 17 nM for K1 *vs*. 43 nM for D10),





being superior to chloroquine (IC_{50} = 540 nM) and slightly better than mefloquine (IC_{50} = 30 nM) (33).

Compounds containing a lactam moiety with 5 different structural classes as potential Pfmrk inhibitors were synthesized and tested against *P. falcifarum*. Compound **50** was the most potent of the series *in vitro*, with an IC_{50} value of 18 μM (34).

Isoquinolines

A series of 26 simple isoquinoline and benzylisoquinolines were tested for antimalarial, antimicrobial, cytotoxic and anti-HIV activities. Compounds **51** and **52** showed antimalarial activity with EC_{50} values of 0.3 and 0.17 μM, respectively (35).

Pyrimidines

The nature of the interactions between *P. falciparum* dihydrofolate reductase and antimalarial antifolates, *i.e.*, pyrimethamine, WR-99210 and some of their analogues, was investigated using molecular modeling in conjunction with the determination of inhibition constants (K_i). The K_i values of several analogues tested support the validity of the model. A "steric constant" hypothesis is proposed to explain the structural basis of antifolate resistance (36). 2,4-Diaminopyrimidine derivatives were synthesized based on inhibition of the S108N and C59R+S108N mutants of dihydrofolate reductase from pyrimethamine-resistant *P. falciparum*. Compound **53** showed *in vitro* activity with IC_{50} values of 0.4 and 1.3 μM for the TM4 and K1CB1 clones, respectively (37).

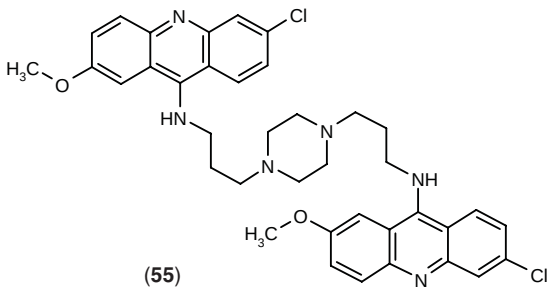
Acridine and bisacridine derivatives

Sulfonamide and urea derivatives of quinacrine with varying methylene spacer lengths were synthesized and tested for inhibition of trypanothione reductase (TyrR) and for activity *in vitro* against strains of the parasitic protozoa *Trypanosoma*, *Leishmania* and *Plasmodium*. Compound **54** showed potent activity *in vitro* with ED_{50} values of 0.0005 and 0.015 μg/ml against *P. falciparum* strains 3D7 and K1, respectively (38).

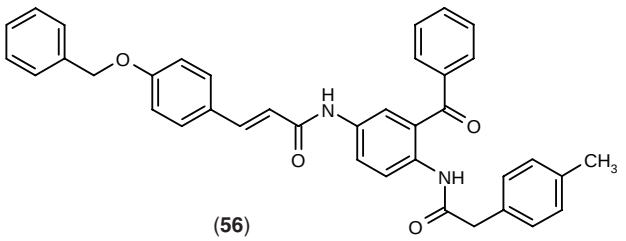
Bis(9-amino-6-chloro-2-methoxyacridines), in which acridine moieties are joined by alkane diamines, polyamines or polyamines substituted by a side chain, were synthesized and tested for their *in vitro* activity against the erythrocytic stage of *P. falciparum*, the trypanomastigote stage of *Trypanosoma bruci* and the amastigote stage of *Leishmania infantum*. Compound **55** showed potent antimalarial activity *in vitro* with an IC_{50} value of 17 nM (39).

Bis(acylamino)benzophenone/cinnamic acid derivatives

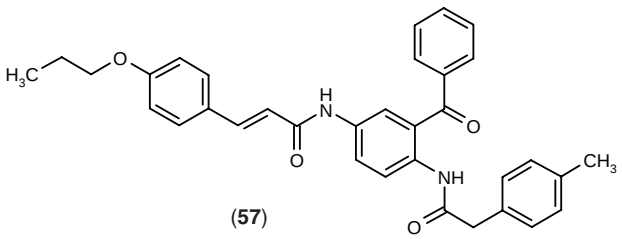
From a library of 61 compounds available from former studies, the 2,5-bis(acylamino)benzophenone **56** was identified as a lead structure for a novel class of antimalarial



(**55**)



(**56**)



(**57**)

agents active against a multidrug-resistant strain of *P. falciparum*, Dd2 (IC_{50} = 0.5 μM for 3D7 and Dd2) (40).

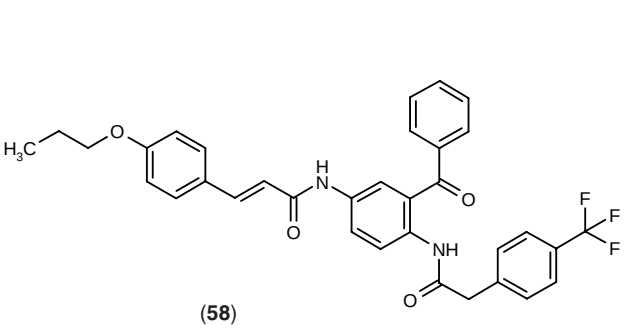
Cinnamic acid derivatives were synthesized and tested for antimalarial activity. Compound **57** showed potent activity *in vitro* with an IC_{50} value of 0.20 μM (41).

N-(4-Acylamino-3-benzoylphenyl)-4-propoxycinnamic acid amide derivatives were synthesized and tested for antimalarial activity *in vitro*. Compound **58** showed potent activity with IC_{50} values of 120 and 100 nM for Dd2 and 3D7 strains, respectively (42).

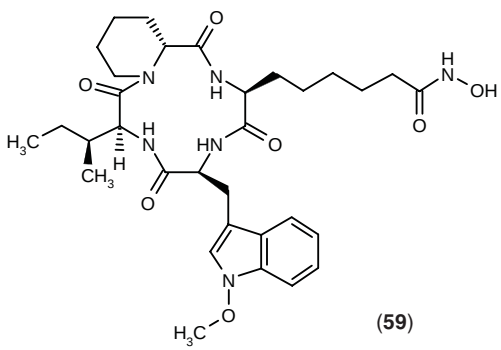
Natural products

Analogues of the natural product apicidin were synthesized and tested for antimalarial activity. Compound **59** showed potent activity with an IC_{50} value of 0.24 ng/ml (43). A series of modified indole moieties were synthesized as well, and compound **60** showed potent antimalarial activity with an IC_{50} value of 15 ng/ml (44).

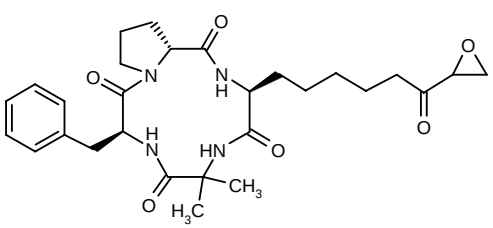
Cyclic tetrapeptoid analogues of apicidin were synthesized and screened for antimalarial activity, and compound **61** showed good activity with an ED_{50} of 0.1 mg/ml (45).



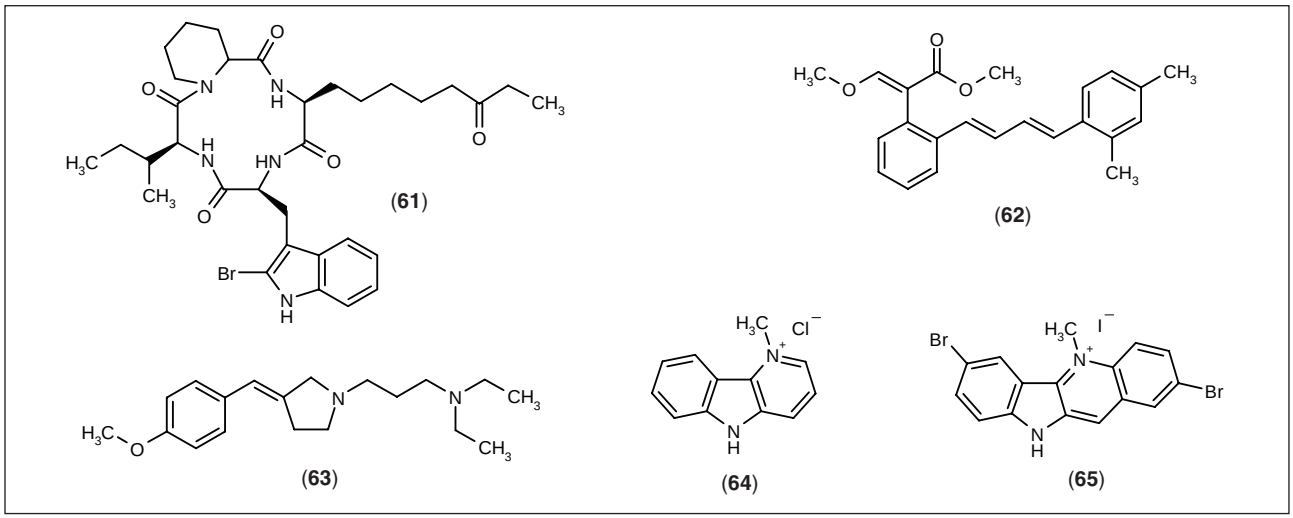
(**58**)



(**59**)



(**60**)



Phenyl β-methoxyacrylates

Phenyl β-methoxyacrylates linked to an aromatic ring via an olefinic bridge have been synthesized and tested for antimalarial activity *in vivo* and *in vitro*. Compound **62** showed potent activity both *in vivo* and *in vitro*, exhibiting ED_{50}/ED_{90} values of 1.11/2.65 mg/kg p.o. and 0.33/0.72 mg/kg i.p. The *in vitro* IC_{50} values obtained for the compound against NF54 and K1 strains were 0.03 and 0.05 ng/ml, respectively (46).

Pyrrolidines

1-[3-(Diethylamino)propyl]-3-(substituted phenylmethylene)pyrrolidines were synthesized and evaluated for chloroquine-resistant reversal activity. The most active compound was **63**, which was shown to inhibit hemeoxygenase by 100% and glutathione-S-transferase by 99% at a dose 15 mg/kg for 5 days (47).

Carbolines

δ-Carbolines, benzo-δ-carbolines, cryptolepines and their salts were synthesized and tested for antimalarial activities *in vitro*. Compound **64** showed potent antimalarial activity with an IC_{50} value of 1.6 μM against the K1 strain (48).

Cryptolepine analogues were tested against *P. berghei* in mice. The most potent was 2,7-dibromocryptolepine **65**, which suppressed parasitemia by 89% as compared to untreated infected controls at a dose of 125 mg/kg/day i.p. (49).

Imidazoles

Peptidomimetic inhibitors of protein farnesyltransferase were synthesized and screened for antimalarial activity. The most active compound was **66** against *P. falcifarum* with an ED_{50} value of 2 μg/ml (50).

Tropolones

A series of compounds bearing an endocyclic -N-O- moiety based on simple derivatives of the tropolone purpurogallin was prepared. Several of these new compounds have activities in the 3-9 μM range. The most active *in vitro* was compound **67** with an IC_{50} value of 3.2 μM (51).

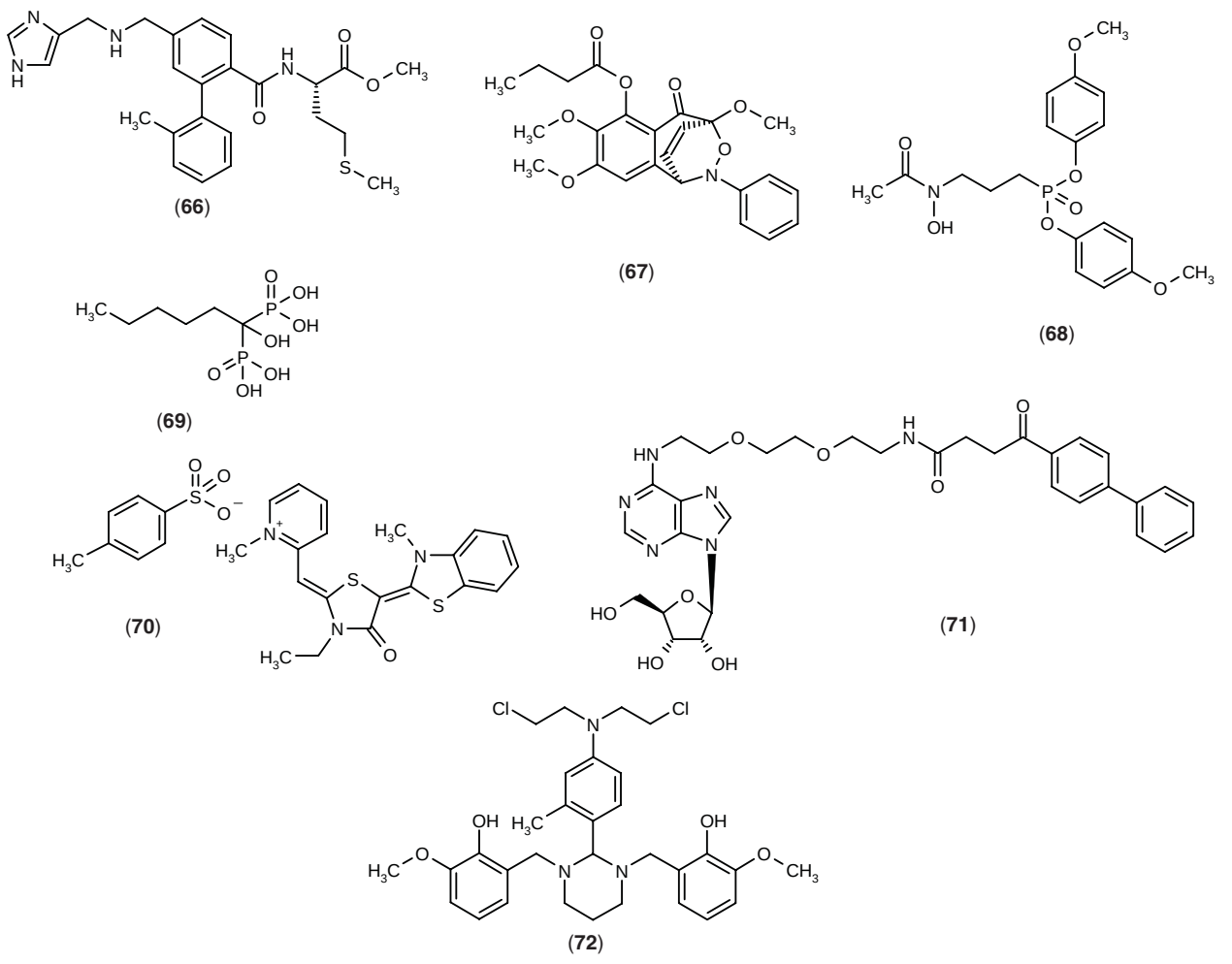
Miscellaneous

Diaryl ester prodrugs of FR-900098 were synthesized and screened for antimalarial activity *in vivo*. Compound **68** showed potent activity in a rodent malaria parasite *P. vinckei* model at 16 mmol/kg (52).

The activity of a series of bisphosphonates against proliferation of *Trypanosoma* species, *Lieshmania donovani* and *P. falciparum* was compared. Compound **69** showed potent antimalarial activity at the intraerythrocytic stage with an IC_{50} value of 5.1 μM (53).

Several rhodacyanine dyes containing a variety of linked heterocyclic moieties were synthesized and their antimalarial potencies evaluated. Compound **70** was the most active with an EC_{50} value of 23 nM (54).

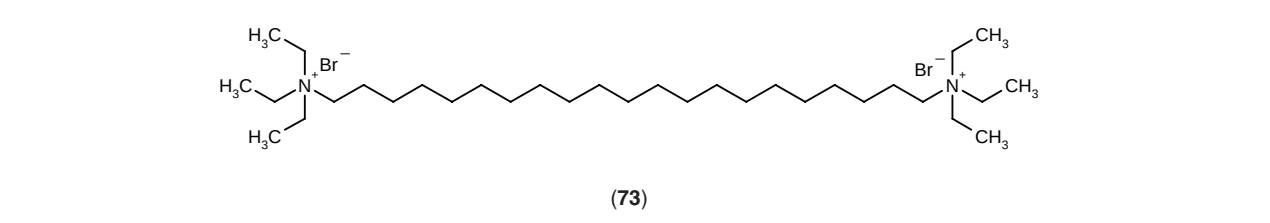
From among a series of N^6-substituted adenosine derivatives, compound **71** showed potent antimalarial activity *in vitro* (IC_{50} = 8 μM) (55). In a serendipitous result, from pharmacophores generated for a database of new non-nucleoside inhibitors of HIV-1 reverse transcriptase, 12 lead compounds were found to be active against the *P. falciparum* strain of malaria. Compound **72** was the most active with an IC_{50} value of 1.2 μM (56).



Cationic choline analogues consisting of mono-, bis- and triquaternary ammonium salts with distinct substituents of increasing lipophilicity were synthesized. The most lipophilic compound was **73** exhibiting an IC_{50} as low as 3 pM (57).

Complications of antimalarial chemotherapy

Antimalarial chemotherapy has become more complex and challenging because of the emergence of multidrug-resistant strains of *P. falciparum*. Chloroquine has been the most important antimalarial for more than 50 years. However, *P. falciparum* strains resistant to chloroquine appeared at the end of the 1950s in South America and Southeast Asia and subsequently spread to most of the Western Pacific islands with evidence of westward spread (58). To combat the drug resistance problem, new synthetic analogs with novel mechanisms of action were developed such as mefloquine, halofantrine and artemisinin derivatives. With the possible exception of artemisinin derivatives (only recently introduced for widespread use in Southeast Asia) (59), resistance has emerged against every antimalarial drug (60-62).



Cross-resistance between compounds of the same class magnifies the problem. Even worse is the emergence of cross-resistance between the newer synthetic analogs mefloquine and halofantrine (63). Mefloquine resistance was reported even before the drug had been routinely used (64, 65), thus severely curtailing its usefulness in some parts of Southeast Asia (66, 67). Halofantrine resistance has emerged concomitantly (68, 69). When atovaquone was used alone in preliminary clinical trials, 28% of the patients had recrudescent infections associated with the development of resistance. Quinine and chloroquine were effective for a long time. However, in many parts of the world, chloroquine is no longer an effective treatment for *P. falciparum* malaria (62) and *P. vivax* has developed resistance. Use of quinine is also threatened in some parts of the world (70).

Conclusions

The main problem with antimalarial chemotherapy is the resistance of parasites to drugs. Parasites resistant to the newly discovered antimalarial drugs have been reported in various parts of world. Until the genomes responsible for resistance are decoded, appropriate resistance reversal agents with distinct mechanisms of action need to be developed. These compounds can make a drug-resistant parasite susceptible to that drug if given in combination. Another strategy is to discover an antimalarial agent whose mechanism of action is completely different from those drugs already available. Such an antimalarial agent could be kept for emergency use. There is also an urgent need to screen large numbers of plant and marine samples to find new potential antimalarial agents with novel structures and different modes of action.

All of these possibilities require R&D activities and, consequently, financial assistance from developed nations to achieve the goal of eradicating malaria worldwide.

Acknowledgements

Three of us (A.K., S.B.K. and A.A.) would like to thank CSIR New Delhi for providing financial support. C.D.R.I. Communication No. 6333.

References

1. Chauhan, P.M.S., Srivastava, S.K. *Present trends and future strategy in chemotherapy in malaria.* Curr Med Chem 2001, 8: 1535-42.

2. Warhurst, D.C. *Antimalarial drug discovery: Development of inhibitors of dihydrofolate reductase active in drug resistance.* DDT 1998, 13: 538-46.

3. Sanchez-Delgado, R.A., Navarro, M., Perez, H., Urbina, J.A. *Toward a novel metal-based chemotherapy against tropical disease 2: Synthesis and antimalarial activity in vitro and in vivo of new ruthenium and rhodium chloroquine complexes*. J Med Chem 1996, 39: 1095-9.

4. Etlinger, H.M., Felix, A.M., Gillessen, D. et al. *Assesement in humans of a synthetic peptide-based vaccine against the sporozoite stage of the human malaria parasite, Plasmodium falciparum.* J Immunology 1981, 40: 626-33.

5. Sweeney, T.R. *Drugs with quinine-like action.* Handbook Exp Pharmacol 1984, 68: 267-324.

6. Wyler, D.J., Oppenheim, J.J. *Lymphocyte transformation in human Plasmodium falciparum malaria.* J Immunol 1974, 113: 449-54.

7. Sweeney, T.R. *The present status of malaria chemotherapy: Mefloquine a novel antimalarial.* Med Res Rev 1981, 1: 281-301.

8. Bruce-Chwatt, L.J., Black, R.H., Canfield, C.J., Clyde, D.F., Peters W., Wernsdorfer, W.H. (Eds.). Chemotherapy of Malaria, 2nd Edition. WHO: Geneva 1986.

9. Sharma, S. *Vector borne diseases.* Prog Drug Res 1990, 35: 365-485.

10. Bell, A. *Recent development in the chemotherapy of malaria.* Curr Opin Anti-infective Invest Drugs 2000, 2: 63-70.

11. Chauhan, P.M.S. *PS-15 Jacobus Pharm Co. Inc.* Curr Opin Anti-infective Invest Drugs 2000, 2: 103-8.

12. Singh, C., Puri, S.K. Indian Patent Application 1583/DEL/99 dt.28.12.99.

13. O'Neill, P.M., Searle, L. et al. *Novel, potent, semisynthetic antimalarial carba analogues of the first-generation 1,2,4-trioxane artemether*. J Med Chem 1999, 42: 5487–93.

14. Li, Y., Zhu, Y.M., Jiang, H.J. et al. *Synthesis and antimalarial activity of artemisinin derivatives containing an amino group.* J Med Chem 2000, 43: 1635-40.

15. Mekonnen, B., Weiss, E., Katz, E. et al. *Synthesis and antimalarial activities of base catalysed adducts of 11-aza-artemisinin.* Bioorg Med Chem 2000, 8: 1111-6.

16. Posner, G.H., Maxwell, J.P., O'Dowd, H. et al. *Antimalarial sulfide, sulfone, and sulfonamide trioxanes.* Bioorg Med Chem 2000, 8: 1361-70.

17. Delhaes, L., Blot, C., Berry, L. et al. *Novel ferrocenic artemisinin derivatives: Synthesis, in vitro antimalarial activity and affinity of bibding with ferroprotoporphyrin.* Bioorg Med Chem 2000, 8: 2739-45.

18. O'Niell, P.M., Miller, A., Bishop, L.P. et al. *Synthesis, antimalarial activity, biomimetic of iron(II) chemistry, and in vivo metabolism of novel, potent C-10 phenoxy derivatives of dihydroartemisinin.* J Med Chem 2001, 44: 58-68.

19. Posner, G.H., Heung, J.P., Jeon, B. et al. *Antimalarial simplified 3-aryltrioxanes: Synthesis and preclinical efficacy/toxicity testing in rodents.* J Med Chem 2001, 44: 3054-8.

20. Hindley, S., Ward, C.A., Storr, R.C. et al. *Mechanism-based design of parasite-targeted artemisinin derivatives: Synthesis and antimalarial activity of new diamine containing analogues.* J Med Chem 2002, 45: 1052-63.

21. Posner, G.H., Northrop, J., Paik, I.H. et al. *New chemical and biological aspects of artemisinin–derived trioxan dimers.* Bioorg Med Chem 2002, 10: 227-32.

22. McCullough, K.J., Wood, J.K., Bhattacharjee, A.K. et al. *Methyl-substituted dispiro-12,4,5-tetraoxanes: Correlations of structural studies with antimalarial activity.* J Med Chem 2000, 43: 1246-9.

23. Opsenica, D., Pocsfalvi, G., Juranic, Z. et al. *Cholic acid derivatives as 1,2,4,5-tetraoxane carriers: Structure and antimalarial and antiproliferative activity.* J Med Chem 2000, 43: 3274-82.

24. Kim, H.S., Nagai, Y., Ono, K. et al. *Synthesis and antimalarial activity of novel medium sized 1,2,4,5-tetraoxacycloalkanes.* J Med Chem 2001, 44: 2357-61.

25. Sundar, N., Jacob, V.T., Valecha, N., Bigwas, S. *Antimalarial t-butylperoxyamines.* Bioorg Med Chem Lett 2001, 11: 2269-72.

26. Hamada, Y., Tokuhara, H., Masuyama, A. et al. *Synthesis and notable antimalarial activity of acyclic peroxides, 1-(alkyldioxy)-1-(methyldioxy)cyclododecanes.* J Med Chem 2002, 45: 1374-8.

27. Murakami, N., Kawanishi, M., Itagaki, S., Horii, T., Kobayashi, M. *New readily accessible peroxides with high antimalarial potency.* Bioorg Med Chem Lett 2002, 12: 69-72.

28. Delarue, S., Girault, S. Maes, L. et al. *Synthesis and in vitro and in vivo antimalarial activity of new 4-aminoquinolines.* J Med Chem 2001, 44: 2827-33.

29. Vennerstrom, J.L., Ellis, W.Y., Agar, A.L. Jr. et al. *Bisquinolines 1. N,N-bis(7-chloroquinolin-4-yl)alkanediamines with potential against chloroquine-resistant malaria.* J Med Chem 1992, 35: 2129-34.

30. Raynes, K., Galatis, D., Cowman, A.F., Tilley, L., Deady, L.W. *Synthesis and activity of some antimalarial bisquinolines.* J Med Chem 1995, 38: 204-6.

31. Vennerstrom, J.L., Ager, A.L., Dorn, A. et al. *Bisquinolines. 2. Antimalarial N,N–bis(7-chloroquinolin-4-yl)heteroalkanediamines.* J Med Chem 1998, 41: 4360-4.

32. Girault, S., Grellier, P., Berecibar, A. et al. *Antiplasmodial activity and cytotoxicity of bis-, tris-, and tetraquinolines with linear or cyclic amino linkers.* J Med Chem 2001, 44: 1658–65.

33. Ayad, F., Tilley, L., Deady, L.W. *Synthesis, antimalarial activity and inhibition of haem detoxification of novel bisquinolines.* Bioorg Med Chem Lett 2001, 11: 2075-7.

34. Xiao, Z., Waters, N.C., Woodard, C.L., Li, Z., Li, P.K. *Design and synthesis of Pfmrk inhibitors as potential antimalarial agents.* Bioorg Med Chem Lett 2001, 11: 2875-8.

35. Iwasa, K., Moriyasu, M., Tachibana, Y. et al. *Simple isoquinoline and benzylisoquinoline alkaloids as potential antimicrobial, cytotoxic and anti-HIV agents.* Bioorg Med Chem 2001, 9: 2871-84.

36. Rastelli, G., Sirawaraporn, W., Sompompisut, P. et al. *Interaction of pyrimethamine, cycloguanil, WR99210 and their analogues with Plasmodium falciparum dihydrofolate reductase: Structural basis of antifolate resistance.* Bioorg Med Chem 2000, 8: 1117-28.

37. Tarnchompoo, B., Sirichaiwat, C., Phupong, W. et al. *Development of 2,4-diaminopyrimidines as antimalarials based on inhibition of the S108N and C59R+s108N mutants of dihydrofolate reductase from pyrimethamine-resistant Plasmodium falciparum.* J Med Chem 2002, 45: 1244-52.

38. Chibale, K., Haupt, H., Kendrick, H. et al. *Antiprotozoal and cytotoxicity evaluation of sulfonamide and urea analogues of quinacrine.* Bioorg Med Chem Lett 2001, 11: 2655-7.

39. Girault, S., Grellier, P., Berecibar, A. et al. *Antimalarial antitrypanosomal and antileishmanial activities and cytotoxicity of bis(9-amino-6-chloro-2-methoxyacridines): Influence of the linker.* J Med Chem 2000, 43: 2646-54.

40. Wiesner, J., Wibner, P. Dahse, H. et al. *Discovery of a novel lead structure for antimalarials*. Bioorg Med Chem 2001, 9: 785-92.

41. Wiesner, J., Mitsch, A.,Wibner, P. et al. *Structure-activity relationship of novel antimalarial agents. Part 2: Cinnamic acid derivatives*. Bioorg Med Chem Lett 2001, 11: 423-4.

42. Wiesner, J., Kettler, K., Jomma, H. et al. *Structure-activity relationships of novel antimalarial agents. Part 3: N-(4-acylamino-3-benzoylphenyl)-4-propoxycinnamic acid amides.* Bioorg Med Chem Lett 2002, 12: 543-5.

43. Colletti, S.L., Myres, R.W., Darkin-Rattray, S.J. et al. *Broad spectrum antiprotozoal agents that inhibit histone deacetylase: Structure-activity relationships of apicidin. Part 1*. Bioorg Med Chem Lett 2001, 11: 107-11.

44. Colletti, S.L., Myres, R.W., Darkin-Rattray, S.J. et al. *Broad spectrum antiprotozoal agents that inhibit histone deacetylase: Structure-activity relationships of apicidin. Part 2*. Bioorg Med Chem Lett 2001, 11: 113-7.

45. Murray, P.J., Kranz, M., Ladlow, M. et al. *The synthesis of cyclic tetrapeptoid analogues of the antiprotozoal natural product apicidin*. Bioorg Med Chem Lett 2001, 11: 773-6.

46. Alzeer, J., Chollet, J., Heinze-Krauss, I., Hubschwerlen, C., Matile, H., Ridley, R.G. *Phenyl β-methoxyacrylates: A new antimalarial pharmacophore*. J Med Chem 2000, 43: 560-8.

47. Batra, S., Srivastava, P., Roy, K., Pandey, V.C., Bhaduri, A.P. *A new class of potential chloroquine-resistance reversal agents for plasmodia: Syntheses and biological evaluation of 1-3'-diethylaminopropyl)-3-(substituted phenylmethylene) pyrrolidines.* J Med Chem 2000, 43: 3428-33.

48. Arzel, E., Rocca, P., Grellier, P. et al. *New synthesis of benzo-δ-carbolines, cryptolepines, and their salts: In vitro cytotoxic, antiplasmodial, and antitrypanosomal activities of δ-carbolines, benzo-δ-carbolines, and cryptolepines.* J Med Chem 2001, 44: 949-60.

49. Wright, C.W., Addae-Kyereme, J., Breen, A.G. et al. *Synthesis and evaluation of cryptolepine analogues for their potential as new antimalarial agents*. J Med Chem 2001, 44: 3187-94.

50. Ohkanda, J., Lockman, J.W., Yokoyama, K. et al. *Peptidomimetic inhibitors of protein farnesyltransferase show potent antimalarial activity*. Bioorg Med Chem Lett 2001, 11: 761-4.

51. Ren, H., Grady, S., Gamenara, D. et al. *Design, synthesis and biological evaluation of a series of simple and novel potential antimalarial compounds*. Bioorg Med Chem Lett 2001, 11: 1851-4.

52. Reichenberg, A., Wiesner, J., Weidemeyer, C. et al. *Diaryl ester prodrugs of FR00098 with improved in vivo antimalarial activity*. Bioorg Med Chem Lett 2001, 11: 833-5.

53. Martin, M.B., Grimley, J.S., Lewis, J.C. et al. *Biphosphonates inhibit the growth of Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondii, and Plasmodium falciparum: A potential route to chemotherapy*. J Med Chem 2001, 44: 909-16.

54. Takasu, K., Inoue, H., Kim, H. et al. *Rhodacyanine dyes as antimalarials. 1. Preliminary evaluation of their activity and toxicity*. J Med Chem 2002, 45: 995-8.

55. Golisade, A., Wiesner, J., Herforth, C., Jomaa, H., Link, A. *Anti-malarial activity of N^6-substituted adenosine derivatives. Part 1.* Bioorg Med Chem 2002, 10: 769-77.

56. Griffith, R., Chanphen, R., Leach, S.P., Keller, P.A. *New anti-malarial compounds from database searching*. Bioorg Med Chem Lett 2002, 12: 539-42.

57. Calas, M., Ancelin, M.L., Cordina, G. et al. *Antimalarial activity of compounds interfering with Plasmodium falciparum phospholipids metabolism: Comparison between mono-and bisquaternary*. J Med Chem 2000, 43: 505-16.

58. Parfitt, K. (Ed.). Martindale The Complete Drug Reference, 32nd Ed. Pharmaceutical Press: London 1999, 422.

59. Hien, T.T., White, N.J. *Qinghaosu*. Lancet 1993, 341: 603-8.

60. *WHO report of an informal consultation*. Geneva, March 14-17, 1994 WHO/MAL/94.1070.

61. Bjokman, A., Phillips-Howard, P.A. *The epidemiology of drug-resistant malaria*. Trans R Soc Trop Med Hyg 1990, 84: 177-80.

62. Wernsdorfer, W.H. *The development and spread of drug resistant malaria*. Parasitol Today 1991, 7: 297-302.

63. Brasseur, P., Bitsindou, P., Moyou, R.S. et al. *Fast emergence of Plasmodium falciparum resistance to halofantrine.* Lancet 1993, 341: 901-2.

64. Brasseur, P., Kouamouo, J., Moyou, R.S., Druilhe, P. *Emergence of mefloquine resistant malaria in Africa without drug pressure.* Lancet 1990, 336: 59.

65. Brasseur, P., Kouamouo, J., Moyou, R.S., Druilhe, P. *Multidrug resistant falciparum malaria in Cameroon in 1987-1988 II. Mefloquine resistance confirmed in vivo and in vitro and its correlation with quinine resistance.* Am J Trop Med Hyg 1992, 46: 8-14.

66. Nosten, F., Ter Kuile, F., Chongsuphajaisiddhi, T. et al. *Mefloquine resistant falciparum malaria on the Thai-Burmese border.* Lancet 1991, 337: 1140-3.

67. Fontanet, A.L., Johnston, D.B., Walker, A.M. et al. *High prevalence of mefloquine resistant falciparum malaria in eastern Thailand.* Bull World Health Organ 1993, 71: 377-83.

68. Basko, L.K. *Type RI resistance to halofantrine in West Africa.* Trop Med Parasitol 1991, 42: 413-4.

69. Ter Kuile, F.O., Dolan, G., Nosten, G. et al. *Halofantrine versus mefloquine in treatment of multidrug-resistant falciparium malaria*. Lancet 1993, 341: 1044-9.

70. Pukrittayakamee, S., Supanaranond, W., Looareesuwan, S., Vanijanonta, S., White, N.J. *Quinine in severe falciparum malaria: Evidence of declining efficacy in Thailand*. Trans R Soc Trop Med Hyg 1994, 88: 324-7.