QUINOLINES AND RELATED COMPOUNDS AS POTENTIAL ANTIMALARIALS

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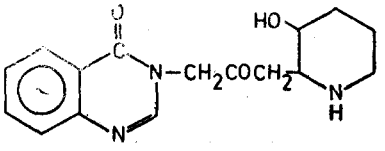
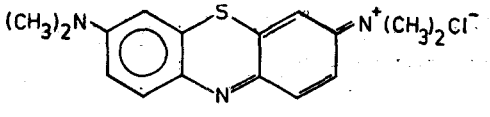
Various 4- and 8- aminoquinoline derivatives having different substituents in the side chain and in the nucleus have been discussed in respect of their antimalarial activity, toxicity and tolerance dosages. The effect of the incorporation of different moieties e.g. piperazine, piperidine and quinoline itself has also been highlighted. Certain quinoline quinones and benzoquinones as effective antimalarial agents have also been described.

Since 1880, when Alphonse Laveran established plasmodium as the causative agent for malaria, man has searched for a remedy for the disease from among the natural products. The chinese drug Febrifuga (I) was one such product isolated from dichroa febrifuga. Pelletier and Caventon isolated



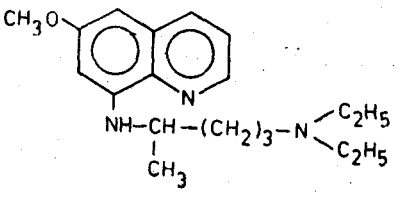
(I)

quinine and cinchonine alkaloids from cinchona bark. After years of reliance on cinchona bark and quinine, the development of synthetic antimalarial, was initiated by German workers, prompted by enemy control of quinine supplies in world war I. Their starting point was methylene blue (II) which had been shown to possess some antimalarial activity.



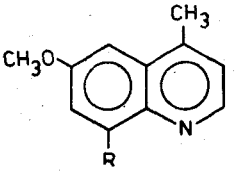
(II)

Structural variations in the methylene blue indicated that a dialkylaminoalkylamino side chain was essential for activity and the researches culminated in the development of the first synthetic antimalarial drug Plasmochin (Pamaquin) III.



(III)

Although it is a potent antimalarial, yet its use is not advised because the margin of safety between therapeutic and toxic dose is too small. Subsequently, in the antimalarial programme for synthesising new drugs, carried out under the Committee on Medical Research, it was found that 8-(6'-diethylaminohexylamino)-6-methoxy lepidine had an extremely high antimalarial activity in avian malaria tests and the introduction of a 4-methyl group (IV) increased the quinine equivalent by about ten folds when tested against Lophurae malaria in duck[1]. (R = Different Dialkylaminoalkylamino side chains.)



(IV)

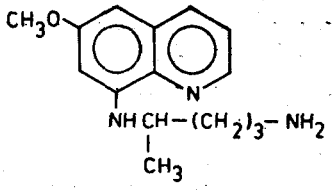
The antimalarial activity together with a toxicity much lower than that of the related quinolines promoted further work in this field. Campbell[2] *et al.* synthesised the products of V ($R=NH_2$) with different 4-substituted alkyles, aldehydes,

alcohols and esters. But as the products had no appreciable antimalarial activity, no further efforts were made to prepare other drugs in this series.

The search for the pamaquine analogue led to the synthesis[3] of 6-β-hydroxy ethoxy-8-diethylaminoalkylaminoquinolines, which are less toxic to the host and yet these retain their therapeutic activity. Other such analogue was 6-methoxy-8-(pseudohelio-tridylamino) quinoline. $2HCl$, which showed slight antimalarial activity[4].

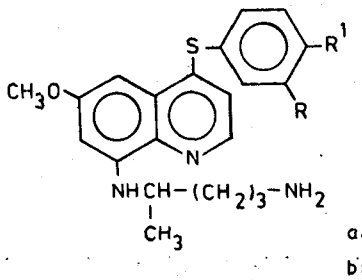
Barett[5] *et al* synthesised the piperazine derivatives of 8-aminoquinoline. Many of the title compounds with terminal nitrogen atoms have high antimalarial activity.

It was observed that the amino-group instead of substituted amino-in the alkylamino side chain of the pamaquine, provided the superior drug primaquine (V), which is particularly effective in preventing relapses and is curative against vivax malaria.



(V)

In view of such an observation, synthesis of 2-benzoyl and 2-benzoylthio analogues of (V) was undertaken[6]. Thioanalogues of primaquine (VI) have also been synthesised[7].

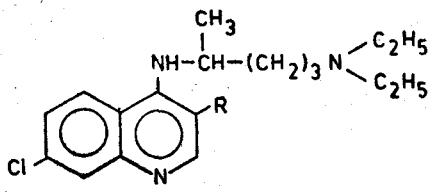


a: R=H, R^1=Cl
b: R=CF_3, R^1=H

(VI)

These derivatives were curative in rhesus monkey against *P. cynomolgi* screen.

Until the early 1940s, the value of 4-aminoquinolines as antimalarial agents was not fully recognised, although they had been developed some ten years earlier in Germany. Resochin, later termed chloroquine (VII, $R=H$), was originally rejected as being too toxic and the attention was therefore turned towards sontoquine (VII, $R=CH_3$). This drug could be given limited clinical trials in Germany and by the French in North Africa, where supplies fell into American hands with the capture of Tunis.



(VII)

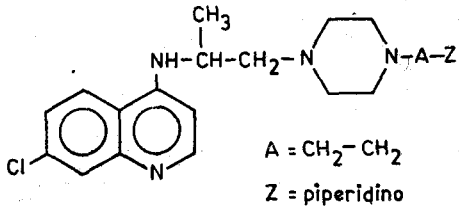
Thus, interest was again aroused in the 4-aminoquinolines and this resulted in the establishment of chloroquine as one of the most effective drugs in antimalarial therapy[8].

In the hope of achieving some positive results with a change in alkylamino-sidechain of chloroquine, Robert synthesised and patented 7-chloro-4-[1-methyl-4-(1-pyrrolidyl) butylamino]-quinoline and its quaternary ammonium salt as valuable antimalarial agent[9].

Tests with hydroxychloroquine on ducks injected with *P. lophurae* showed that it was 5 times as effective as quinacrine at 20 mg/kg. It has also less toxicity as compared to other 4-aminoquinolines[10].

The incorporation of the piperazine in the alkylamino-side chain of chloroquine resulted in the synthesis of useful antimalarial agents, 1-[2-(7-chloro-

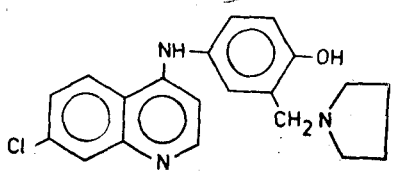
4-quinolyl) aminopropyl] -4-(2-piperidinoethyl) piperazine (VIII) possessed antimalarial activity".



(VIII)

Further modification in (VIII) with the inclusion of substituted phenyl ring[12] or different quinoline derivatives[13] instead of piperidino yielded products of appreciably high antimalarial activity.

A slight variation in camoquine, by cyclising the two ethyl groups, resulted in amopyraquine (IX) which was less toxic than chloroquine and useful particularly when injected intramuscularly. It has optimum antimalarial activity and low toxicity[14].



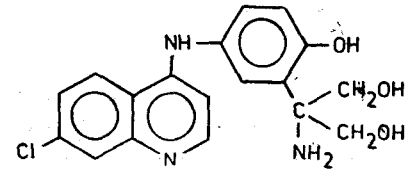
(IX)

The significant role of the alkylamino-side chain with various alterations resulting in the useful drugs encouraged other workers[15] to synthesise the 4-aminoquinolines with quaternary carbon side chains. One of these compounds, 7-chloro-4-(3-amino-2, 2-dimethylpropylamino) quinoline, was found active when tested on mice infected with a lethal dose of *P. berghei.*

Quinoline compounds containing quinuclidine ring in the side chain were also prepared and tested for their antimalarial activity against *P.berghei* in mice. 7-Chloro-4-(3-oxoquinuclidinyl-2-methylene amino) quinoline and 7-chloro-4-(3-hydroxy-quinuclidinyl-2-methyleneamino) quinoline were curative[16].

Chloroquine derivatives with unsaturation in the diamine side chain in the form of acetylenic and *cis* and *trans* ethylenic bonds were prepared and their antimalarial activity was compared with Chloroquine. It was observed that some were more potent and less toxic than chloroquine[17].

With a view to synthesise camoquin analogue with quaternary side chain, Natrajan *et al*[18] have prepared 4-[3-(α, α-dihydroxy-methylaminomethyl) -4'-hydroxyphenyl-amino]-7-chloroquinoline (X), which showed antimalarial activity against *P. bergbei* in mice at a minimum effective dose of 10 mg/kg.

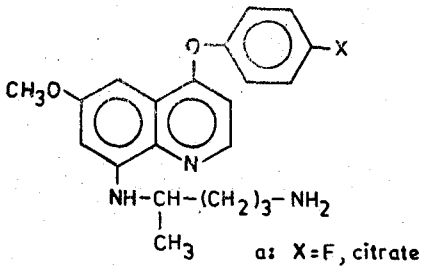


(X)

Elslager *et al*[19] prepared a series of 4-[(7-chloro 4-quinolyl)amino] -α-[(diethylamino)-0-cresolesters] and amide derivatives. Most of the compounds exhibited noteworthy activity and protected mice against *P. berghei* for 2-4 weeks at 400 mg/kg.

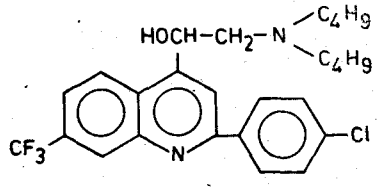
Pamaquin was known to prevent the incidence of malarial relapses, which could not adequately be done by 4-aminoquinolines and thus interest was focussed once more on 8-aminoquinolines with a view to decreasing the toxicity and increasing the effectiveness of pamaquin. Subsequently pentaquine and primaquine were found to be the least toxic and most effective 8-aminoquinolines. Other modifications in pamaquin were made by additional substitution at various positions. 4-(4'-Chlorophenoxy)-6-methoxy-8-nitro quinoline and 8-(5-amino-1-methyl pentylamino)-6-methoxy lepidine diphos-

phate were synthesised and evaluated for their antimalarial activity. Both of these were superior to primaquine with no toxicity at 640 mg/kg and the latter at 1 mg/kg was curative against *P. eynomolgi* in the rhesus monkey[20]. This observation prompted the other workers[21] to bring out modified primaquine with alterations at 4-and 8-positions. The compounds (XI) thus prepared were not toxic at 640 mg/kg and the most active compound was (XIa). In the monkey antimalarial screen (XIa) and (XIb) produced radical cure.



(XI)

Various fluorine containing α-dialkylaminomethyl-2-phenyl-4-quinoline methanols were prepared for evaluation against *P. berghei*. It was observed that the F-compounds were more potent than the corresponding Cl-derivatives. One of these compounds, α -(dibutylaminomethyl)-2-(4-chlorophenyl)-7-trifluoromethyl-4-quinolinemethanol, (XII)was curative in mice[22].



(XII)

2, 8-Bis-(trifluoromethyl)- α -(2-piperidyl)-4-quinoline methanol also showed curative effect at 20 mg/kg against *P. berghei* in mice[23].

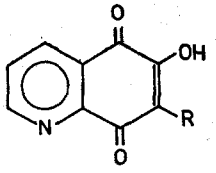
Andrew[24] *et al* prepared and evaluated many of 2-benzoyl-4-quinoline methanols and observed that these were generally more potent antimalarials and less phototoxic than the corresponding 2-phenyl analogues.

Series of 2-quinolinemethanols with Cl-substitution at various positions in the quinoline nucleus were synthesised. One such compound, α—di-*n*-butyl-aminomethyl-4-(4-chlorophenyl) 6, 8-dichloro-2-quinolinemethanol-*HCl* was curative against *P. berghei* in mice. It extended the mean survival time by 6.3 days at 640 mg/kg[25].

Mefloquine, a 4-quinolinemethanol containing trifluoromethyl group has been recently reported to be most potent antimalarial[26].

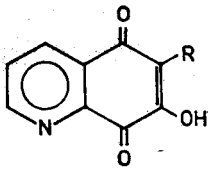
Brassi[27], *et al* observed the antimalarial activity of natural, racemic and synthetic dihydroquinine, dihydro quinidine and their various racemic analogues in mice infected with *P. berghei*. It was found that (±)-dihydroquinine hemisulfate and its optical antipodes were as active as quinine. *HCl* at 200 mg/kg (minimum effective oral dose), whereas dihydroquinidine-hemisulfate, 6′-demethoxy-7′ chlorodihydroquinidine dihydrochloride were 4 times more active at minimum effective oral dose 50 mg/kg.

A group of workers switched over to the synthesis of quinolinequinones. 7-Alkyl-6-hydroxy-5, 8-quinoline quinones (XIIIa) and 6-Alkyl-7-hydroxy-5,



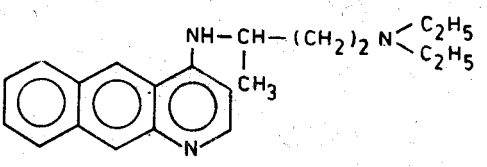
(XIII a)

8-quinoline quinones (XIIIb) were prepared and evaluated against *P. berghei* in mice, at 160-220 mg/kg. XIIIa ($R=(CH_2)_{14}CH_3$) was found to be an active compound[28].



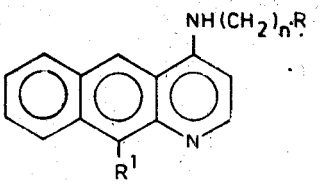
(XIII b)

A group of Russian workers[29,30] synthesised new benzoquinoline derivatives and one of these derivatives; debaquine (XIV) has been proved to be antimalarial, even superior to chloroquin. Thus a series of benzoquinolines.



(XIV)

(XV) and their N-oxides were prepared and one such compound (R=cyclopentylamino, $R^1=H$, $n=3$) was found to have the highest chemotherapeutic coefficient.



(XV)

REFERENCES

1. CAMPBELL, K.N., ELDERFIELD R.C., *et al., J. Am. Chem. Soc.*, **69** (1947), 1465.
2. CAMPBELL, K.N., RAYMOND, A. LAFORGE & BARBARA, K. CAMPBELL, *J. org. Chem.*, **14** (1949), 346.
3. MARCUS, S. MORGAN & CRETCHER, L.H., *J. Am. Chem. Soc.*, **68**, (1946), 781-4.
4. MENSHIKOV, G.P., *J. Gen. Chem.* (*USSR*), **17** (1947), 1714-17; *Chem. Abst.*, **42**, (1948), 2599a.
5. BARETT, P.A., CALDWELL A.G. & WALLS, L.P., *J. Chem. Soc.*, (1961), 2404-18.
6. SHETTY, R.V., *et al., J. Med. Chem.*, **20** (1977), 1349-51.
7. TANABE, *et al., J. Med. Chem.*, **21** (1977), 133-136.
8. ANDERSAY, BREITNER & JUNG, *U. S. Patent*, 2233970; *Chem. Abst.*, **35** (1941), 3771.
9. ROBERT, H. REITSEMA, *U. S. Patent*, 2526417; *Chem Abst.*, **45** (1951), 2511g.
10. MIGNEL NIETO-CAICEDO, *Am. J. Trop. Med. Hyg.*, **5** (1956), 781-5; *Chem. Abst.*, **53** (1959), 20534a.
11. RHONE-POULENC, S.A., *Belg.*, 645602, *Chem. Abst.*, **63** (1965), 11588g.
12. RHONE-POULENC, S.A., *Neth. Appl.*, 6,413,687; *Chem. Abst.*, **64** (1966), 9745h.
13. RHONE-POULENCE, S.A., *Belg.*, 618068, *Chem. Abst.*, **59** (1963), 6370b.
14. NOBLES, W.L., *et al., J. of Pharm. Sci.*, **52** (1963), 600-1.
15. PEARSON, D.E., & CRAIG, J.C., *J. Med. Chem.*, **10** (1967), 737.

16. SINGH, TARA, STEIN, R.G., *J. Med. Chem.*, **10** (1967), 737.

17. SINGH, TARA, STEIN, R.G., BIEL, J.H., *J. Med. Chem.*, **13** (1969), 368-71.

18. NATRAJAN, P. N., *et al., J. Med. Chem.*, **15** (1972), 329-30.

19. ELSLAGER, EDWARD, F., *et al., J. Med. Chem.*, **12** (1969), 600-7.

20. LAMONTAGNE, M.P., MARKOVAC, ANICA & MENKA, J.R., *J. Med. Chem.*, **20** (1977), 1122-7.

21. CHEN, ENGENE, H., *et al., J. Med. Chem.*, **20** (1977), 1107-8.

22. ANDREW, KAZUOKATA & TOYOKAIYA, *J. Med. Chem.*, **11** (1968), 277-81.

23. LUTZ, R.E., OHNAMACHT, C.J., PATEL, A.R., *J. Med. Chem.*, **14** (1971), 928-9.

24. ANDREW, J., SAGGIOMO, *et al., J. Med. Chem.*, **15** (1972), 989-94.

25. MARKOVAC, A., STEVENS, C.L. & ASH, A.B., *J. Med. Chem.*, **15** (1972), 490-3.

26. DAVIDSON, M.W., *et al., Nature*, **254** (5501), (1975), 632-4.

27. BROSSI, A., *et al., Experientia*, **27** (1971), 1100-1; *Chem. Abst.*, **76** (1972), 101c.

28. PORTER, THOMAS *et al., J. Med. Chem.*, **14** (1971), 1029-33.

29. BEKHLI, A.F., *et al., Med. Parazitol. Parazit. Bolezni*, **46** (1977), 71-2; *Chem. Abst.*, **87**, (1977), 68120r.

30. KOZYREVA, N.P., BEKHLI, A.F., *et al., Khim. Farm. Zh.*, **12** (1978), 73-7; *Chem. Abst.*, **88** (1978), 43071d.