A Review on Recent Developments In The Synthesis of Quinoline Derivatives As Antimalarial Drugs

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Abstract- *Quinolines and their derivatives are well known for their diverse biological activities such as antibacterial, antifungal, anti-inflammatory, anticancer, antiviral, antidiabetic and anti-tuberculosis activities, along with potent antimalarial activity. Therefore, the synthesis of new chemical compounds containing quinoline scaffolds has increased in recent years. This review summarizes the recent developments carried on quinoline based antimalarial drugs.*

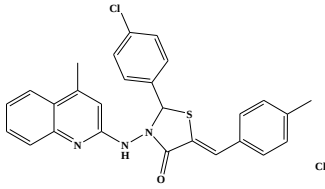
Keywords- Antimalarials, Chloroquine, Plasmodium falciparum, Quinoline.

I. INTRODUCTION

Antimalarial drugs are drugs used to prevent and treat malaria. Quinine, chloroquine, amodiaquine, artemether, halofantrine, proguanil, and lumefantrine, and the antimalarial antibiotic doxycycline are some of the drugs that are effective against the asexual erythrocytic stages of malaria parasites. While primaquine is the only drug used against the exoerythrocytic forms of the parasite. Although several classes of antimalarial drugs are currently available, but their overall therapeutic efficacy has been reduced due to toxicity issues and the emergence of drug-resistant malaria parasites. Quinoline-based antiplasmodial drugs have undoubtedly been long established and continue to inspire the design of new antimalarial agents. So in recent years a lot of research on quinoline based antimalarial drugs has been carried out. This review summarizes the recent developments carried on quinoline based antimalarial drugs.

II. ANTIMALARIAL ACTIVITY

Jain et al have synthesized a novel series of quinoline-thiazolidinone hybrids where compound **1** exhibited promising in vitro antimalarial potency against both 3D7 and RKL-9 strains of *Plasmodium falciparum*.[1] Further, during in vivo antimalarial screening compound **1** showed highest suppression of parasitemia against P. berghei.



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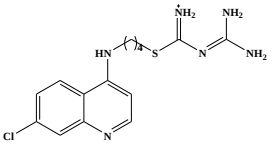

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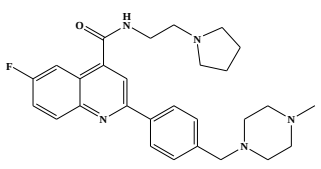
As guanylthiourea (GTU) has been identified as an important antifolate antimalarial pharmacophore unit, Bhagat et al have synthesized 4-aminoquinoline - Guanylthiourea hybrids and screened for their antimalarial activity.[2] In vitro analysis of these synthesized compounds reveal that out of the nine molecules, eight show antimalarial activity in the range of 0.61-7.55 μM for PfD6 strain and 0.43-8.04 μM for PfW2 strain. Compound **2** showed highest activity with IC_{50} value of 0.6 μM against Pf D6 strain and 0.4 μM against Pf W2 strain.



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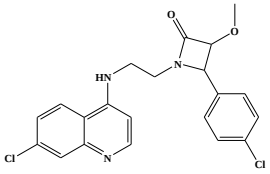
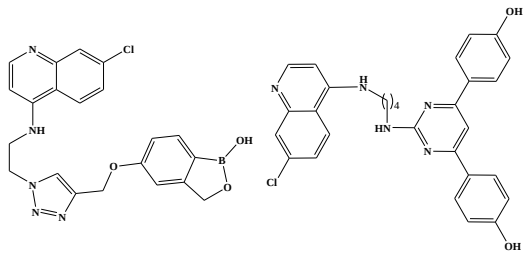


4

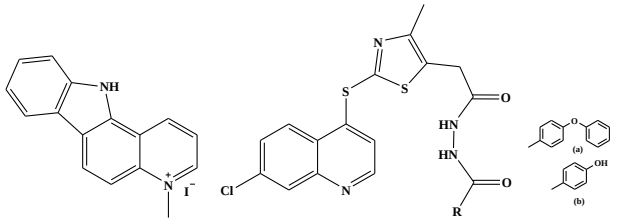
Hochegger et al have reported the synthesis and antiplasmodial activity of some 2,4-disubstituted 6-fluoroquinolines.[3] Compound **3** showed high in vitro activities against PfNF54 strain with IC_{50} of 0.0029 μM and a multidrug resistant strain (PfK1) with IC_{50} of 0.002 μM and extended the number of mean survival days (MSD = 16) remarkably compared to control (MSD = 6–7). Tukulula et al have reported a second generation of 4-aminoquinoline- and 8-aminoquinoline-based tetrazoles and lactams **4** and were subsequently evaluated in vitro for their antiplasmodial activity against a multidrug-resistant K1 strain.[4] Most of them displayed good antiplasmodium activities with IC_{50}

values of 0.20-0.62 µM that were comparable to the reference drugs.



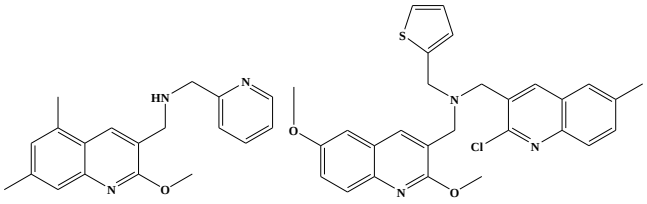
5 **6**

1*H*-1,2,3-triazole-tethered 4-aminoquinoline-benzoxaborole hybrids and aryl substituted benzoxaborole analogues were synthesized and screened for their anti-plasmodial efficacy against both chloroquine-susceptibility 3D7 and chloroquine-resistant W2 strains of *Plasmodium falciparum*.[5] 4-aminoquinoline-benzoxaborole conjugate **5** with ethyl as spacer exhibited IC_{50} values of 4.15 and 3.78 µM against 3D7 CQ-susceptible and W2 CQ-resistant strains of *Plasmodium falciparum* with lower cross resistance with chloroquine. Kayamba et al have synthesised a series of novel *N*-(7-chloroquinolin-4-yl)-*N'*-(4,6-diphenylpyrimidin-2-yl)alkanediamine hybrids and evaluated their antimalarial activity against the NF54 chloroquine-susceptible strain.[6] The activity result data revealed that seven analogues showed promising to good activity with IC_{50} values of 0.32 µM-4.30 µM. Compound **6** showed the most prominent activity with IC_{50} value of 0.32 ± 0.06 µM along with a favourable safety profile of 9.79 to human kidney epithelial (HEK293) cells. Further compound **6** exhibited the highest binding affinity for both PfHsp70s with KD in a lower nanomolar range (4.4-11.4 nM).



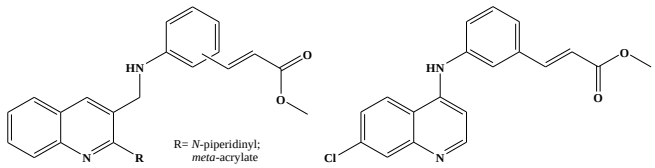
7 **8**

Håheim et al have prepared a series of quinoline-based tetracyclic ring-systems **7** and evaluated for their in vitro antiplasmodial activity against *Plasmodium falciparum* strain.[7] Two compounds showed the best antiplasmodial activity against the *Plasmodium falciparum* 3D7 strains with IC_{50} values of 128 nM and 380 nM. Ramírez et al have designed and synthesized twelve 7-chloroquinoline derivatives and were tested as antimalarials.[8] Some of them showed an efficient in vitro activity as inhibitors of β-hematin formation and an in vivo activity in a murine model, resulting in compounds **8a** and **8b** as the most active ones with IC_{50} values of 0.65 ± 0.09 and 0.64 ± 0.16 µM, respectively.



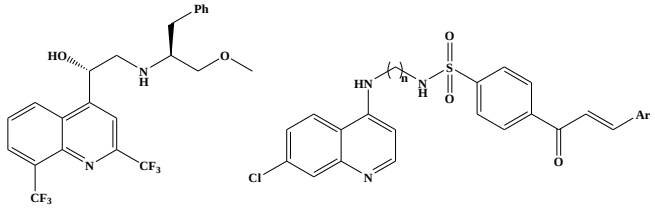
9 **10**

A series of mono- and bisquinoline methanamine derivatives were synthesised and the resulting compounds were investigated for in vitro antiplasmodial activity against the 3D7 chloroquine-sensitive strain of *Plasmodium falciparum* by Bokosi et al.[9] Compounds **9** and **10** showed the most promising IC_{50} values of 0.23 and 0.93 µM, respectively. Further, compounds 9 and 10 were also evaluated in silico by molecular docking protocols for binding affinity to the fast-growing face of a hemozoin crystal model.



11 **12**

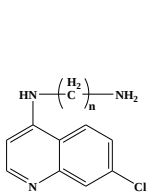
Bokosi et al also designed and synthesized a series of 2-(N-cyclicamino)quinolines coupled with methyl (E)-3-(2/3/4-aminophenyl)acrylates and screened in vitro for potential antiplasmodial activity against a chloroquine-sensitive (3D7) strain of *Plasmodium falciparum*.[10] Compound **11** exhibited the highest antiplasmodial activity with IC_{50} value of 1.4 µM. Further Bokosi and Ngoepe also reported a series of nine hybrid compounds of 7-substituted 4-aminoquinoline and cinnamic acid as antiplasmodial agents.[11] All the compounds showed moderate activity, with IC_{50} values ranging from 1.8 to 16 µM against the Pf3D7 chloroquine-sensitive strain. Compound **12** was most potent with an IC_{50} value of 1.8 µM.



13 **14**

Five new series of total fifty-two compounds of aminoalcohol quinolines were designed, synthesized and evaluated in vitro against Pf3D7 and PfW2 strains by Dassonville-Klimpt et al.[12] Among them, compound **13** was found as a promising antimalarial candidate with IC_{50} values

of 14.9 nM and 11.0 nM against respectively Pf3D7 and PfW2 and a selectivity index higher than 770. Vinindwa et al have reported the use of molecular hybridization to generate new molecular hybrids and the resultant hybrids were tested against the chloroquine sensitive (NF54) strain of *Plasmodium falciparum*.[13] The synthesized compounds displayed good antiplasmodial activity with IC_{50} values ranging at 0.10–4.45 µM. Fluoro substituted derivative **14** showed more potency as compared to the unsubstituted molecular hybrid.



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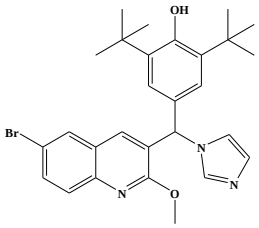
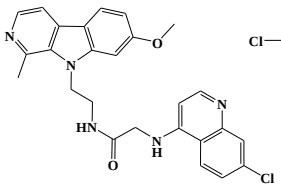


16

Mosquito-borne diseases and the lack of effective treatments are causing a significant increase in the incidence of such diseases worldwide. In this view, Murugan et al have reported a new 4,7-dichloroquinoline derivative showing significant larvicidal and pupicidal properties against a malarial and a dengue vector with a lethal toxicity ranging from 4.408 µM/mL (larva 1) to 7.958 µM/mL (pupae) for Anopheles stephensi and 5.016 µM/mL (larva 1) to 10.669 µM/mL (pupae) for Aedes aegypti.[14] Compound **15** revealed a significant growth inhibition of both sensitive strains of Plasmodium falciparum with IC_{50} values of 6.7 nM (CQ-s) and 8.5 nM (CQ-r) as compared to Chloroquine IC_{50} values of 23 nM (CQ-s), and 27.5 nM (CQ-r). Roy et al have synthesized a series of quinoline-imidazole hybrid compounds and evaluated their blood-stage antimalarial activity in both drug-sensitive and -multi drug-resistant (MDR) Plasmodium falciparum strains.[15] Compound **16** exhibited significant in-vitro antimalarial efficacy against both CQ-sensitive (IC_{50}- 0.14 µM) and MDR strain (IC_{50}- 0.41 µM) with minimal cytotoxicity and high selectivity.



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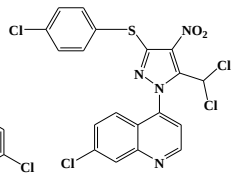
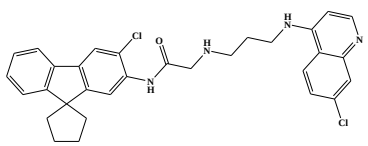


18

Poje et al have synthesized harmiquin hybrids and its antiplasmodial activity was evaluated against the erythrocytic stage of the Plasmodium life cycle.[16] Compound **17** displayed single-digit nanomolar IC_{50} value against Pf3D7 (IC_{50} = 2.0 ± 0.3 nM). It showed significantly higher activity than CQ against the resistant Plasmodium strains with a very high selectivity index (4450). Zapol'skii et al have prepared a series of 26 novel 1-(7-chloroquinolin-4-yl)-4-nitro-1*H*-pyrazoles bearing a dichloromethyl and an amino or thio moiety and their antimalarial activity was evaluated in vitro against the protozoan malaria parasite Plasmodium falciparum.[17] Notably, compound **18** inhibited the growth of the chloroquine-sensitive Plasmodium falciparum strain 3D7 with IC_{50} value of 0.2 ± 0.04 µM.



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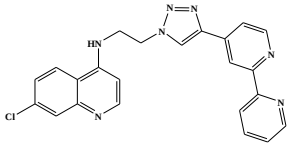
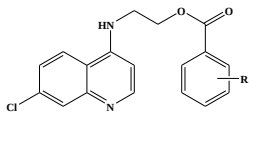


20

Parth et al have identified fluorene-chloroquine hybrids as a new promising class of antiplasmodial agents.[18] Compound **19** exhibited good *in vitro* antiplasmodial activity against a chloroquine-sensitive NF54 strain of the human malaria parasite Plasmodium falciparum with an IC_{50} value of 139 nM. Sovari et al have reported the synthesis of a series of aminoquinoline- and IMP-based 1,2,3-triazole ligands and their corresponding Re(I) complexes and screened for their antimalarial activity against the CQS (NF54) and MDR (K1) strains of Plasmodium falciparum.[19] The most promising candidate, compound **20** displayed an IC_{50} value (0.098 ± 0.008 µM) comparable to CQ in the MDR K1 strain.



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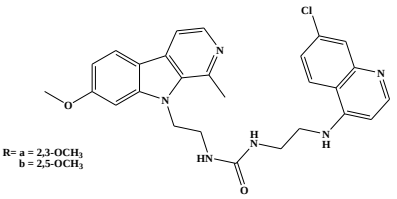
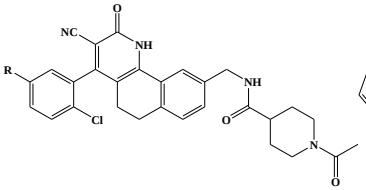


22

A series of heterocyclic chloroquine hybrids have been synthesized and screened for its antimalarial activity against chloroquine-sensitive strains of Plasmodium berghei ANKA by Gutiérrez et al.[20] The compounds significantly reduced haeme crystallization, with IC_{50} values < 10 µM. The values were comparable to chloroquine's, with an IC_{50} of 1.50 ± 0.01 µM. The compounds **21a** and **21b** prolonged the average survival time of the infected mice to 16.7 ± 2.16 and 14.4 ± 1.20 days, respectively. Pavić et al reported the synthesis and evaluation of the biological activity of new hybrid compounds, ureido-type (UT) harmiquins, based on chloroquine (CQ) or mefloquine (MQ) scaffolds and β-carboline alkaloid harmine against cancer cell lines and Plasmodium falciparum.[21] Screening of the antiplasmodial activities of UT harmiquins against erythrocytic stages of the

Plasmodium life cycle identified CQ-based UT harmiquine **22** as a novel antiplasmodial hit because it displayed low IC_{50} values in the submicromolar range against CQ-sensitive and resistant strains (IC_{50} 0.06 ± 0.01, and 0.19 ± 0.02 μmol L-1, respectively), and exhibited high selectivity against Plasmodium, compared to mammalian cells.



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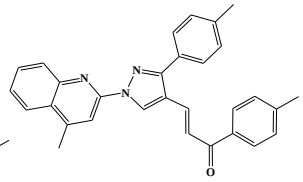
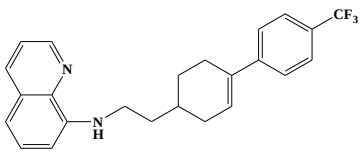


24

Ibrahim et al have synthesized tetrahydrobenzo[h]quinoline chemo type derivatives **23** and evaluated for their antileishmanial, antimalarial and antitubercular activities.[22] Most of the compounds exhibited promising antiplasmodial effect against P. berghei with suppression percentage of up to 97.78%. The most active compounds were further screened in vitro against the chloroquine resistant strain Plasmodium falciparum, (RKL9) and showed IC_{50} value range of 0.0198-0.096 μM, compared to IC_{50} value of 0.19420 μM for chloroquine sulphate. Kumar et al have reported a novel series of pyrazolyl chalcones containing quinoline scaffold and evaluated for their significant antimalarial potential against CQ-sensitive and CQ-resistant strain of Plasmodium falciparum.[23] Compound **24** was found to be the most potent among the series of synthetic analogues.



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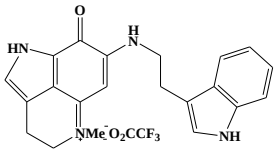
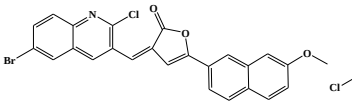


26

Half the world's population has malaria because resistance to antimalarial drugs is a major obstacle. To overcome this, Sharma et al have synthesized a new series of substituted 4-phenyl-1,2,3,6-tetrahydropyridine (THP) 8-aminoquinoline-based hybrid analogs.[24] Out of thirteen, four compounds have exhibited good antimalarial activity against chloroquine-sensitive (3D7) and chloroquine-resistant (RKL-9) strain with the minimum inhibitory concentration. Compound **25** was the most effective and showed consistently good potency against the drug-resistant (RKL-9) strain. Barnes et al have developed an efficient synthesis of the PIQ alkaloids and evaluated against drug-resistant strains of *Plasmodium falciparum* and four human cell lines.[25] The results revealed that imine N-methylated makaluvamines and analogues **26** are extremely potent antiprotozoal agents



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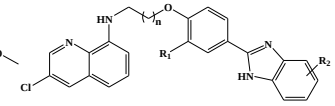

28

To combat resistance against current antimalarial drugs, medicinal chemists need to develop a large number of new pharmacophores that enable them to combat drug resistance. In this view, Choudhary et al have designed and synthesized bulkier quinoline-furanone hybrids and screened for their bioactivity against the resistant strain of Plasmodium through Schizont maturation inhibition assays.[26] Among them, compound **27** exhibited superior LDH inhibition compared to chloroquine CQ while other three compounds have showed IC_{50} values comparable to CQ and moderate LDH inhibition. Krstulović et al have synthesized 7-chloro-4-aminoquinoline-benzimidazole hybrids **28** and were tested for their effects on the growth of the non-tumor cell line MRC and carcinoma, leukemia, and lymphoma cell lines.[27] Further, the antiplasmodial activity of these hybrids was evaluated against two Plasmodium falciparum strains (Pf3D7 and PfDd2).

III. CONCLUSION

Quinoline and their derivatives possess broad spectrum of biological properties such as antibacterial, antifungal, anti-inflammatory, anticancer, antiviral, antidiabetic and anti-tuberculosis activities, along with potent antimalarial activity. Quinoline-based antiplasmodial drugs have undoubtedly been long established and continue to inspire the design of new antimalarial agents. So this review summarizes the recent developments carried on quinoline based antimalarial drugs.

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