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Recent Developments in the Side Chain Modified 4-Aminoquinolines As Anti-malarial Agents

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Abstract: The 4-aminoquinolines are considered to be one of the most vital synthetic antimalarial agents. However, control of malaria is threatened by inadequate resources and drug resistance particularly to this class of compounds. In order to overcome this barrier, various chemical modifications in the 4-aminoquinoline moiety have been attempted to accomplish new analogs with promising antimalarial properties against sensitive as well as resistant strains of *P. falciparum* with minimal undesirable side effects. This review describes essentially some of the recent advances made in the last nine years on chemical modifications of 4-aminoquinolines along with a brief description of biological evaluation. It is interesting to note that simple modifications have led to compounds having potent activity against CQ-R strains and some of these molecules are in clinical trials.

Keywords: 4-Aminoquinolines; Resistant strains; Side-chain modifications.

Abbreviations: CQ: chloroquine; CQ-S: chloroquine-sensitive; CQ-R: chloroquine-resistance: SAR: structure-activity-relationship; I.P: intraperitoneal; 4-AQ: 4-aminoquinoline; *P. falciparum*; plasmodium falciparum.

1. Introduction

Malaria is one of the most common infectious diseases of the tropics caused by the genus *Plasmodium* [1]. According to World Health Organisation, it is estimated that in 2013, 3.4 billion people were at risk, and 97 countries had ongoing malaria transmission. The most effected population includes those living in the tropical regions, especially south Asia and Africa. Majority of malaria deaths occur in sub-Saharan Africa, mostly children under five years of age [2]. Malaria remains the major public health problem in India. Northeastren region of India is one of the hot spots for malaria transmission. Focal outbreaks of malaria are common occurrence especially forest fringed villages of Assam, bordering Arunachal Pradesh

[3]. Orissa alone contributes to more than 40% of *falciparum* deaths in India, south Orissa is know as hyper-endemic area of the state [4].

Malaria is caused by five species of the genus *Palsmodium* that effect humans namely *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*. Among these *P .falciparum* is the most lethal form and it predominates in Africa [5]. *P. falciparum* infection leads to cerebral malaria with multiple systemic complications like unarousable coma, severe anemia, repeated seizures and hepatopathy. *P. vivax* is less dangerous but more widespread; *P. ovale* and *P. malariae*, represent only a small percentage of infections. Malaria caused by these three parasites is called benign malaria. However, chronic infections with *P. malariae* can result in a nephrotic syndrome [6]. *P. knowlesi* species that infect primates has lead to human malaria but the exact mode of transmission remains uncertain [7].

One of the major obstacle in the adequate control of malaria has been limited the therapeutic options available for its treatment. The current commonly used classes of drugs are limited to aminoquinolines and other derivatives such as arylamino alcohols, biguanides, diaminopyrimidines and endoperoxides. Chloroquine and primaquine have been extensively used for the treatment and prophylaxis of malaria respectively [8]. However, widespread drug resistance to available therapeutic agents and the emergence of multi-drug resistant strains has resulted in limited treatment options [9]. Therefore, to meet the new challenges development of novel molecules with better therapeutic potential and safety is a very high priority task. So far, malaria control has relied largely on a small number of chemically related drugs, belonging to three classes of compounds: Quinoline and its related analogs (quinine, CQ, amodiaquine, primaquine, mefloquine, and halofantrine), the artemisinin and its derivatives (artemisinin, artesunate, artemether, arteether, dihydroartemisinin), the antifolate compounds (pyrimethamine, proguanil, chlorcycloguanil, dapsone, and sulfadoxine), and hydroxy-1,4-napthoquinone (atovaquone) [10].

During the past five decades, 4-aminoquinolines have been the mainstay for malaria chemotherapy. The success of the 4-aminoquinoline based drugs particularly chloroquine has been due to its clinical efficacy, ease of use, low-cost and affordability [11]. However, the rapid spread of parasite resistance to chloroquine and other available antimalarial drugs is the major hurdle to treat malaria. This has led to renewed interest in search of new chemical entities effective against multi drug-resistant strains of malaria parasite. Towards this objective good number of research publications including reviews have appeared in the literature during the past one decade [12-13]. Therefore it was thought appropriate to collate these observations so as to enable more focussed research activity culminating in the discovery of new molecule to meet the present challenge in malaria chemotherapy. This review mainly focuses on the biological evaluation of the novel side-chain modified 4-aminoquinolines during the period 2005 to 2014.

1.1 Life cycle of malaria parasite

The life cycle of plasmodia has five stages that include both sexual and asexual mode of reproduction in two hosts, namely a mosquito and a human as shown in Fig 1. During a blood meal, a malaria-infected female Anopheles mosquito injects sporozoites into the human host. These sporozoites then migrate to the liver where they transform, multiply, and mature into tissue schizonts, which eventually rupture, releasing merozoites into the blood stream. To avoid the host's immune system, they invade erythrocytes. After the initial

replication in the liver, the parasites undergo asexual multiplication in the erythrocytes (erythrocytic stage). In every cycle, schizonts get ruptured within erythrocytes and release new merozoites into the blood stream, which in turn again invade the new erythrocytes. Before this stage the infected individual may not have any symptoms, once RBCs get ruptured, the host immune system get exposed to parasite factors in turn stimulates to release cytokines and results in the symptoms like fever and chill. In case of *P. vivax* and *P. ovale*, a dormant hypnozoite stage remains in the liver and causes relapse by invading the blood stream, weeks to years later. After a number of asexual life cycles, some merozoites develop into sexual erythrocytic forms (gametocytes). When an Anopheles mosquito ingests male and female gametocytes during a blood meal from an infected host, fertilization takes place in the gut of the mosquito forming zygotes. The zygotes become elongated and invade the gut wall of the mosquito developing into oocysts. These oocysts grow, rupture, and release sporozoites. These invade the mosquito's salivary gland, and the mosquito is then ready to transmit the disease during the next blood meal [1].

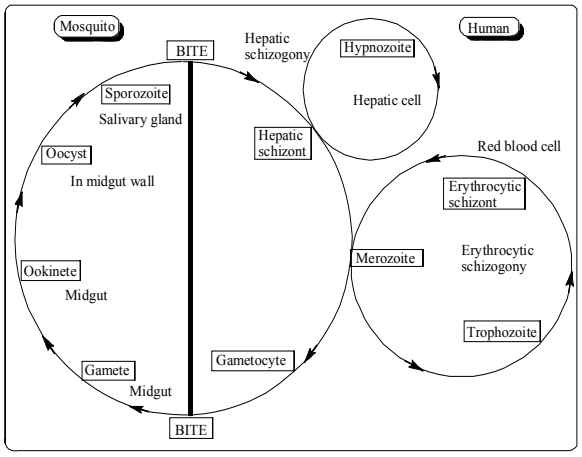


Figure 1-Life cycle of malaria parasite

1.2 Structure activity relationship studies on 4-aminoquinoline

Chloroquine (CQ), a 4-aminoquinoline derived compound has dominated the malaria chemotherapy for more than five decades. Findings of the early structure-activity studies on the 4-aminoquinoline scaffold have led to identification of minimum structural elements essential for antimalarial activity as shown in Fig 1.1 which shows a quinoline nucleus attached to a basic side chain, arrows indicate the specific site of modifications and their contributions to the biological activity. Replacement of the 7-chloro group by electron-withdrawing and/ or electron-donating groups has led to decrease in the activity [14]. Basicity of the quinoline ring nitrogen (pKa_1) and the side chain terminal nitrogen (pKa_2) is essential for activity and the optimal activity is elicited when the range is 8.1 and 10.2 respectively [15]. The role of carbon chain length in the aminoalkyl side chain has also been investigated, and the results suggested that both shortening (2-3 carbon) and lengthening (10-12 carbon) of the diaminoalkane side chains in the CQ led to retaining the antimalarial activity [16]. In the present discussion, we have focused only the significant highlights on the structure activity relationship of the side-chain modified 4-aminoquinolines.

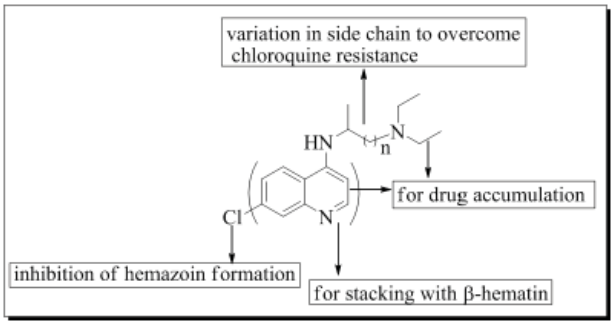
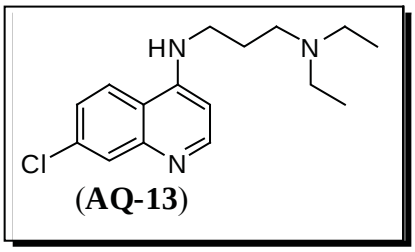


Figure 1.1- General structure of 4-aminoquinolines

1.3 Side-chain modification on 4-aminoquinoline

Development of parasite resistance to CQ has led to renewed interest in the structure-activity

studies on the 4-aminoquinoline scaffold. Two seminal biochemical observations have further catalysed the research activity, viz., CQ undergoes N-deethylation to give the desethyl compound as a major metabolite which has the same activity as CQ against sensitive strains, but reduced activity against CQ-resistant strains [15]. Secondly and more importantly, biochemical studies have suggested that parasite resistance to CQ is compound specific but not scaffold specific. This has encouraged the researchers to focus primarily on modification of the side chain to obtain molecules with improved therapeutic activity against CQ resistant strains. By taking into account the above facts, Krogstad *et al.* synthesized lead compound AQ-13 shown in Fig 1.1.1 Currently this molecule is in Phase II clinical trails [17].



(**AQ-13**)

Figure 1.1.1- Structure of AQ-13

Based on the observation that the dialkylamino side-chain on 4-aminoquinoline undergoes oxidative dealkylation, and this can be prevented by introducing metabolically more stable rings on the side-chain, Sparatore group prepared new componds having a bulky, strongly basic, and lipophilic bicyclic quinolizidine moiety and tested *in vitro* against CQ-S and CQ-R strains of *P. falciparum* and *in vivo* in *P. berghei* mouse model. The quinolizidine ring was linked either directly to the 4-amino group (n=0) or through a methylene spacer (n=1-3). All the tested compounds showed promising activity against CQ-R strain (IC_{50} between 21 and 94 nM). The activity was reduced by increasing the number of methylene groups between the aminoquinoline and the quinolizidine moiety. Compound **1** (n=0) was the most active compound of the series with an IC_{50} of 21.27 nM against K1 strain [18]. They have also explored pyrrolizidinylalkyl derivatives of 4-amino-7-chloroquinolines (**2**). These compounds exhibited high activity against both CQ-R strains of W-2 and K1, being 2.5 to 10 fold more active than CQ. The *in vivo* studies, in the murine *P. berghei* malaria model, showed that analogues **2a-b** behaved similarly to CQ in the single-dose treatment. Particularly, **2a** at 10.0 mg/kg produced a mean survival of 25.7 and 29.3 days, respectively and 2/3 mice were cured [19]. Compound 2a has been selected for further study as a promising antimalarial agent. Faruk Khan *et al.* [20] incorporated isoquinuclidine ring system to CQ and synthesized semirigid analogues **3** and **4** respectively. These analogues were tested against CQ-S (D6) and CQ-R (W2) strain of *P. falciparum*. Compound **3** displayed 2-fold potent activity against CQ-S and about 30-fold more potent activity against CQ-R than chloroquine. Analogue **4a** also exhibited activity as potent as chloroquine against the D2 and about 7-fold more potent against W2 strains. Ryckebusch and co-workers synthesized N^1-(7Chloro-4-quinolyl)-1,4-bis(3-aminopropyl) piperazine derivatives (**5**) and tested against CQ-R strain. They have introduced different bulky and hydrophobic groups in the side-chain, but there is no improved activity against CQ-R. Whereas, by adding substituents like cyclic tertiary amino group the antimalarial activity was increased 10-20 folds against CQ-R as observed in the case of compounds **5a-b** with an IC_{50} values of 6.5 and 11.6 nM, respectively [21]. S. Gemma *et al*. examined antiplasmodial activity of new antimalarial heterodimers (**6**) based on the 1,4-bis(3-aminopropyl)piperazine linker and evaluated against CQ-S and CQ-R *P. falciparum*. Among the compounds tested in this study, **6a** was found to be the most potent molecule, exhibiting 16 and 8-fold more activity than CQ against K1 and W2 strains respectively

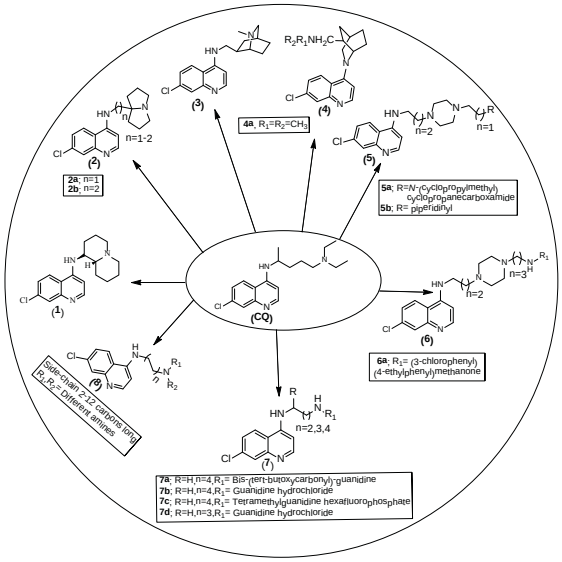


Figure 1.1.2- Variations at the side chain of chloroquine having bulkier moitfs

[22]. From the SAR studies, it is well established that pKa of the side chain amino group plays an imporatant role in antimalarial activity. Towards this objective from this laboratory, Solomon group explored new analogues by introduction of Boc, guanidine, and tetramethylguandine moieties (**7**) which would highlight the basicity at the lateral side chain of nitrogen. These analogues were tested for *in vitro* antimalarial activity against the CQ sensitive NF-54 strain of *P. falciparum*. Based on *in vitro* potency, compounds **7a-d** were selected for *in vivo* activity against CQ-resistant N-67 strain of *P. yoelii* in Swiss mice at 30.0 mg/kg by i.p route [23]. Among the tested compounds, compound **7b** showed 88.98% suppression on day 4. Hocart and co-workers reported 108 AQs, including 68 newly synthesized molecules (**8**) were assessed for biological evaluation. All compounds were active against both CQ-S and CQ-R *P. falciparum* strains. They proposed some structural features to determine the antiparasitic activity by using computational QSAR studies. Side chains ranged from 2 to 12 carbons, and terminal side chain amine functions included $(Me)_2N$, $(ethyl)_2N$, $(propyl)_2N$, $(butyl)_2N$, pyrrolidines, piperidines, azepanes, azocanes, primary amines, secondary amines, and unsymmetrical linear secondary amines [24]. The *in vitro* inhibitory activities of these AQs against CQ-S and CQ-R *P. falciparum* strains (Haiti 135 and Indochina I, respectively) were interpreted based on their IC_{50} values (AQs with IC_{50}s of ≤ 25 nM were considered active).

It is well established that pK_a of the quinolyl nitrogen atom as well as the basicity in the side chain of CQ are vital for antimalarial activity. Towards this objective Natarajan *et al*. synthesized several derivatives (**9**) to study the effect of altering the pK_{a1} of the quinolyl nitrogen by replacing with the alkoxy (**9a**) or alkylthio (**9b**) substituents. An additional amino group was also introduced to the side-chain of the 4-oxo analogues (**10**). The removal of the 4-amino group by either an alkylthio or an alkoxy substituents generally reduced the potency against CQ-R strain with an IC_{50} ranged from 1.8 to 9.5 μM. On the other hand, introduction of an additional basic amino group to the side-chain of the 4-oxo CQ analogues improved the potency versus both the CQ-S and CQ-R strains with an IC_{50} ranged from 0.04 to 1.4 μM [25]. In a similar manner, Solomon *et al.* also studied the effect of quinoline ring nitrogen (pK_{a1}) of 4-amioquinoline derivatives. In order to evaluate this concern a new series of compounds bearing N^{ω}-oxide in the quinoline ring (**11**) were synthesized and also accessed pK_{a1} values. The targeted compounds were tested for biological assay against NF-54 strain of *P. falciparum* in *in vitro* for the determination of minimum inhibitory concentration. All compounds displayed MIC range between 0.27 and 4.32 μM. Compounds **11a-c** displayed significant activity, and the same were selected for *in vivo* activity. The compounds **11a-c** suppressed 56.76, 59.49, 48.23% parasitaemia on day 4 respectively. Another important finidng was observed that pK_{a1} values of the tested compounds drastically decreased compared to

chloroquine pK_{a1}. Albeit, it has been observed that N^{ω} oxide modification on quinoline ring affect the antimalarial activity in *in vitro* as well as *in vivo*. This study also reveals the importance of quinonyl ring nitrogen, which is essential for both transportation of the molecule through the memberane as well as for binding to hematin [26]. Similarly, Iwaniuk *et al*. [27] prepared new set of compounds by systematic modification of the chain length as well as the basicity in the side chain of CQ. Many of these analogs have exhibited promising antiplasmodial activity against HB3 and Dd2 strains. Compounds **12** and **13** having low resistance indices values are the most potent of this series. Roepe *et al.* [28] envisioned the incorporation of an increasing number of basic amino groups carrying a branched or a linear side chain with two or three amino functions of the aliphatic side chain attached to the 4-amino-7-chloroquinoline (**14-17**). All the synthesized compounds were evaluated against four different strains of *P. falciparum.* Many of these derivatives exhibited excellent antimalarial activity against CQ-S and CQ-R strains. The tribasic, 4-amino-7-chloroquinolines (**14a-b**) comprise a short linear side chain with two additional aliphatic tertiary amino functions were the most active analogues with IC_{50} values of 31.2 and 28.1 nM, respectively. The common structural features of amidoquine and mefloquine are having a basic nitrogen proximity to a hydroxy group. Since at physiological pH, the basic nitrogen will be protonated, it is possible that the intramolecular hydrogen bonding between the protonated amine, and the hydroxyl may be an important feature for activity against chloroquine-resistant *P. falciparum*. Based on this postulation, Guy *et al*. synthesized a series of compounds **18** and **19** containing four different alkyl linkers and various aromatic substitutions with hydrogen bond accepting capability. All the synthesized compounds exhibited broad potency against drug-resistant W2 strain of *P. falciparum*. In particular, a novel series containing variations of the α-aminocresol motif was active against the W2 strain [29].

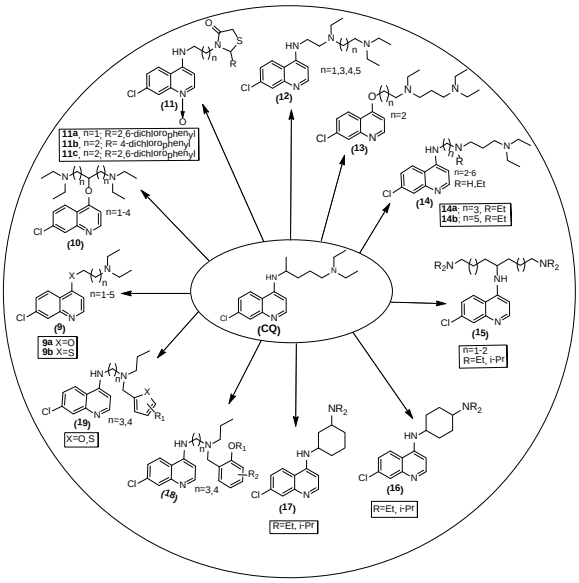


Figure 1.1.3- Variations at the side chain of chloroquine having alkyl/aromatic substituents

Solomon *et al.* [30] studied the effect of antimalarial activity on 4-aminoquinolines by complete removal of the basicity of the tertiary nitrogen on the pendent amino group with thiazolidine-4-one nucleus. The basis of this modification was to prevent dealkylation without affecting the lipophilicity and antimalarial activity of the 4-aminoquinolines. All the compounds **20-23** were evaluated for their antimalarial activity. Interestingly, most of the compounds showed promising *in vitro* activity against the NF-54 strain of *P. falciparum*. The compounds **20a-b** and **22a-b** displayed significant activity ranging from 0.013-0.271μM. These compounds were selected for *in vivo* studies (Swiss mice) against *P. yoelli* (N-67 strain), treated with 30 mg/kg through i.p route. Compounds **20a-b** and **23a** suppressed 76.08, 81.00 and 62.32% parasitaemia on day four compared to 100% suppression displayed by CQ. Chauhan and co-workers synthesized, 4-aminoquinoline and rhodanine based derivatives (**24** and

25) respectively. Among tested compounds, compounds **24a** and **25a-c** showed very good antimalarial activity with IC_{50} values ranging from 13.2 to 45.5 nM against CQ-R (K1) strain. Overall, compound **25c** displayed nanomolar activity against resistant strain of *P. falciparum* with IC_{50} value of 13.2 nM [31]. Sunduru *et al*. [32] examined new prototypes by incorporating motifs like thiourea, thiazolidinedione and thioparabanic acid on the side chain of 4-amino-7-chloroquinoline. The synthesized derivatives **26-28** were evaluated for *in vitro* antimalarial activity against CQ-S strain of *P. falciparum*. Thiourea derivatives (**26**) showed good antimalarial profile of IC_{50} ranging from 6.07 to 42.02 ng/mL and thiazolidinedione (**27**) showed moderate activity with IC_{50} in the range of 11.03–111.61 ng/mL, while thioparabanic acid derivatives showed below moderate activity of 33.08–199.31 ng/mL when compared to chloroquine. Based on *in vitro* efficacy and selectivity index compounds **26a-b** and **27a** were screened in an *in vivo* model against chloroquine resistant N-67 strain of *P. yoelii* in Swiss mice at 50 mg/Kg/day for 4 days by intraperitoneal route (i.p). Out of three evaluated compounds, thiourea derivative (**26a**) found to be the most active against chloroquine resistant strain with 99.27% suppression on day 4 and 50.50% suppression on day 10. In similar manner Soloman and colleagues explored a set of 4-aminoquinolines in which lateral side chain of diethyl amino functionality was modified with a variety of heterocyclic rings substituted thiourea functionality including pyrrolidinyl, piperidyl, morpholinyl, piperazinyl and substituted piperazinyl. These derivatives (**29**) exhibited promising *in vitro* antimalarial activity against the CQ-S (D6) and CQ-R (Dd2) strains of *P. falciparum*. Among them, compound **29a** exhibited superior *in vitro* activity with IC_{50} value of 14.1 nM against resistant strains of *P. falciparum* as compared to CQ [33]. Mahajan *et al*. [34] explored the antimalarial activity of 4-amino-7-chloroquinolinyl thiourea derivatives (**30**). The most active compound from the series **30a** displayed an inhibitory IC_{50} value of 1.2 μM against the D10 strain of *P. falciparum*. Ekoue-Kovi *et al.* [35] explored more than fifty 4-amino-7-chloroquinoline derived sulfonamides, ureas, thioureas, and amides. Several analogues showed promising antimalarial activity and low resistance indices. Among evaluated compounds **31-35**, sulfonamide (**31a**) containing a short side chain with a terminal dansyl moiety produced high antiplasmodial potency with an IC_{50} of 18 and 23 nM against HB3 and Dd2 strains respectively. Musonda *et al*. [36] synthesized a new series of 4-aminoquinoline γ- and δ-lactams (**36**) via the Ugi 3-component 4-centre multicomponent reaction and tested against chloroquine-resistant W2 strain of *P. falciparum*. It was observed that the size of the lactam ring was responsible for the antiplasmodial activity. Usually compounds having six-membered lactam ring were more active than the five-membered ring. Compound (**36a**) exhibited antimalarial activity with an IC_{50} of 0.096 μM (2.5- fold to CQ). Compounds having β-amino alcohol moiety showed potent antimalarial activity. On the other hand, the oxazolidinone ring can be viewed as a rigid form of the β-amino alcohol moiety. Based on these postulations, Kobarfard and co-workers synthesized aminoquinoline-based aminoalcohols (**37**) and oxazolidinones (**38**). Targted compounds evaluated for *in vitro* antiplasmodial activity against CQ-S and CQ-R strains. β-amino alcohol derivatives (**37a-c**) showed promising activity against CQ-S strain with IC_{50} values 9, 0.8 and 6 nM, respectively, and remarkable activity against CQ-R strain. Whereas, oxazolidinones derivatives displayed moderate activity in the case of CQ-S strain and exhibited significant activity against CQ-R strain [37].

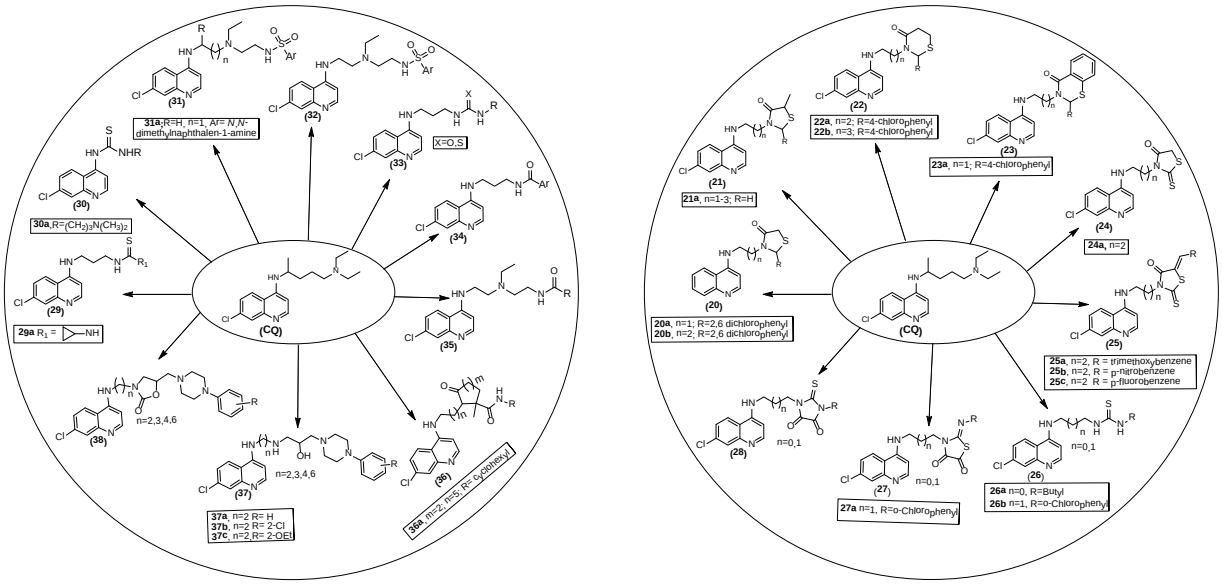


Figure 1.1.4 and **Figure 1.1.5** - Variations at the side chain of chloroquine having thiazolidinedione, thiourea, thioparabanic and oxazolidinones substituents

Blackie *et al*. [38] synthesized two phenylequine analogues (**39** and **40**) and tested against CQ-S (D10) and CQ-R (K1) strain *in vitro*. These two analogues exhibited increased efficacy in both the strains. The *in vivo* efficacy was determined for compound (**39**) in *P. berghei* ANKA and *P. yoelii.* It has displayed an ED_{50} of 0.81 mg/kg (i.p x 4days) in *P. yoelii*. Ray and co-workers designed a library of new molecules based on the 4-aminoquinoline related structure of CQ. ADMET prediction studies were employed to assess lead molecules. Compounds **41** and **42** with promising *in vitro* activity with improved ADMET properties, and desirable pharmacokinetic profiles were identified as lead molecules. Both **41** and **42** are highly potent antimalarial compounds with IC_{50} values of 5.6 and 17.3 nM, respectively against the CQ-R (W2) strain of *P. falciparum* when compared to CQ with IC_{50} value of 382 nM [39]. Solaja and co-workers synthesized 4-aminoquinolines bearing steroidal and adamantyl components. The SAR showed that the compounds with an amide functionality linking the 4-amino-7-chloro moiety to the steroid or adamantyl were inactive. Whereas, the 4-amino-7-chloro with two ionizable amino groups were more potent than mono amino analogues. The most active compounds were adamantyl derivative (**43**) and steroidal derivative (**44**) with an IC_{50} value of 8.4 and 3.38 nM, respectively [40]. Chiyanzu *et al.* [41] synthesized aminoquinoline-isatin derivatives for biological evaluation against three strains of the malaria parasite *P. falciparum*. They introduced ethylene linker (**44**) and piperzine linker (**45**) between the 4-aminoquinoline and isatin. Compounds having ethylene linker in the molecules showed good antimalarial activity compared to piperzine linker. Quinoline thio semicarbazone derivatives generally showed better inhibition compared to the corresponding ketones. Moreover, non-quinoline Mannich base thiosemicarbazones were less active compared to the corresponding quinoline Mannich bases. Substitution at position 5 on the isatin ring plays an important role for antiplasmodial activity. Chloro (compound **46a**) and methyl (compound **46b**) substitution at position 5 exhibiting promising activity against K1 with an IC_{50} value of 0.054 μM (6-fold to CQ), and 0.051 μM (5-fold to CQ) against K1 and W2 strains respectively. Soloman and

group synthesized EDTA-4-aminoquinoline conjugates (**47**) and evaluated for antimalarial efficacy against the *P. falciparum* strain of NF-54 *in vitro*. All compounds displayed moderate activity. Furthermore, EDTA esters displayed good efficacy than the corresponding acids [42].

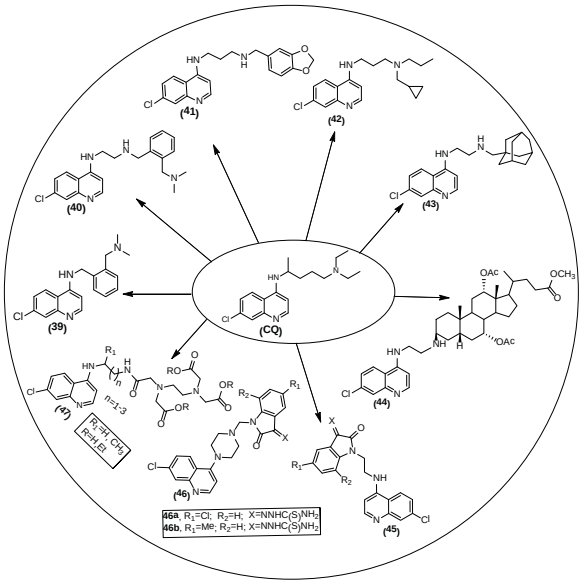


Figure 1.1.6 - Variations at the side chain of chloroquine having aromatic, adamantyl, steroidal and isatin substituents

The antimalarial activity of 4-aminoquinoline containing 2,4,5-trisubstituted aminoxazoles (**48** and **49**) were synthesized via multicomponent reactions and tested against two strains of the *P. falciparum* parasite *in vitro* by Musonda *et al* [43]. All tested compounds exhibited good to moderate activity. Molecules with alkyl spacer have shown better activity than piperazine linker. Compound **48a** displayed 21-fold efficacy against CQ-S, 54-fold more potent than chloroquine with an IC_{50} of 0.019 μM in the case of CQ-R and **48b** exhibited 8-fold and 28-fold against CQ-S and CQ-R strains, respectively. Compound **49a** displayed promising activity with an IC_{50} value of 0.36 μM, while lowest activity was observed with **49b** derivative. Sinha and colleagues synthesized new 4-amino-7-chloroquinoline derivatives (**50** and **51**) by using different α, β^3-and γ-amino acids linked to various alkyl amines and tested against *in vitro* antimalarial activity. Most of the synthesized molecules displayed excellent selectivity indices as well as resistance index compared to CQ. This series of compounds acts heme polymerization target. Compounds **51a-b** showed 4.6 and 3.6 fold antimalarial activity against CQ-R strains with an IC_{50} values of 55.29, 71.16 nM, respectively [44]. Molecules having β-carboline motif were found to exhibit antimalarial activity. These analogos inhibit the DNA synthesis of the malarial parasites. Keeping these observations, Gupta *et al.* [45] synthesized a series of hybrid molecules 2-[3-(7-chloro-quinolin-4-ylamino)-alkyl]-1-(substituted phenyl)-2,3,4,9-tetrahydro-1H-b-carbolines (**52**) and tested for *in vitro* antimalarial activity against CQ-S strains of *P. falciparum*. Some of the derivatives **52a-c** exhibited MIC in the range of 0.05–0.11μM and found to be several folds more active than CQ. It has been observed that molecules possessing phenolic Manich base as well as thio semicarbazone components displayed significant antimalarial activity. These components are also members of a class of iron-chelators. It is well known that iron-chelating agents inhibit parasite growth. Chipeleme group synthesized a series of phenolic Mannich bases of benzaldehyde and (thio) semicarbazone derivatives. The synthesized molecules (**53**) evaluated *in vitro* against the malarial cysteine protease falcipain-2 and a chloroquine resistant strain (W2) of *P. falciparum*. Compound **53a** was the most potent antimalarial with an IC_{50} of 0.077 μM against W2 [46]. By introducing aryl/heteroaryl substrates with piperazine on the side chain of aminoquinolines Kumar *et al*. [47] synthesized a set of compounds **54-56** and tested for *in vitro* activity against NF 54 strain of *P. falciparum*. All the synthesized compounds exhibited MIC in the range of 0.031 to 10 μg/mL. Compound **54a** (MIC = 0.125 μg/mL) was equipotent to standard drug CQ (MIC = 0.125 μg/mL) and compound **55a** (MIC =

0.031 μg/mL) was 4-fold more potent than CQ. Compound **54a** showed the curative response to all the treated swiss mice infected with CQ-resistant N-67 strain of *P.yoelii* at the doses 50 mg/kg and 25 mg/kg for four days by i.p route and was found to be orally active at the dose of 100 mg/kg for four days. From the activity data, it clearly demonstrated that propyl linker was favorable for the antimalarial activity.

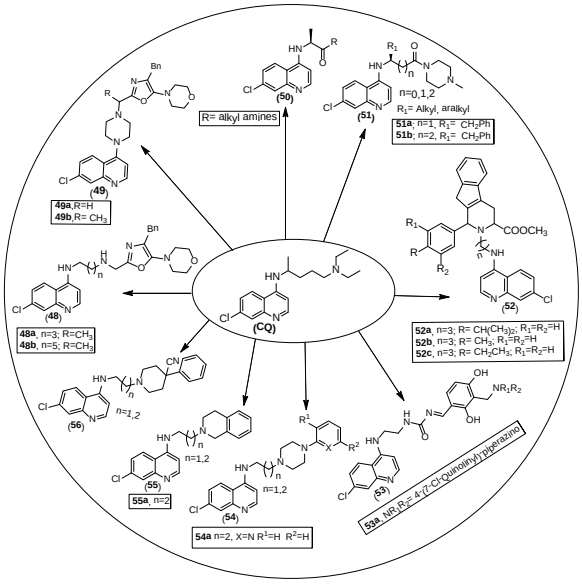


Figure 1.1.7 - Variations at the side chain of chloroquine having aminoxazoles, aminoacids, β-carboline, adamantyl, steroidal and isatin substituents.

Bouillon *et al*. [48] explored new 4-Aminoquinolines by 3-(2,2,2-Trifluoroethyl)-γ-hydroxy-γ-lactam motif in the side chain. Later, synthesized derivatives **57-59** were evaluated *in vitro* activity against *P. falciparum* strains 3D7 and W2 respectively. These molecules displayed potent *in vitro* activity with IC_{50} values in the range from 19-50 nM. In the entire set, the most promising compounds **59a-b** displayed remarkable IC_{50} values close to 26 and 19 nM against the CQ-S strain and 49 and 42 nM against MDR strain. By using similar approach, Kanishchev and group examined new series containing key intermediate of 5-(arylthio- and heteroarylthio)-methylene)-3-(2,2,2-trifluoroethyl)furan-2(5H)-ones, this was reacted with 4-aminoquinoline-derived amines via ring opening-ring closure process affording the corresponding γ-hydroxy-γ-lactams. The resulting new 4-aminoquinoline-lactams (**60**) were evaluated against *P. falciparum* of 3D7 and W2 strains and found to be active in the range of 89-1600 nM [49]. Perez and group explored series of cinnamic acid-4-aminoquinoline conjugates namely, HEDICIN heterocyclic-dipeptide-cinnamic acid conjugates (**61**), HECIN, heterocyclic-cinnamic acid conjugates (**62**), and assessed their *in vitro* antiplasmodial activity aganist CQ-R strain. HECIN derivatives (**62**) did not display remarkable activity. Whereas, in the case of HEDICIN derivatives, compound **61a** bears a bulky electron-donating p-isopropyl group and did not inhibit heme polymerization *in vitro*, but displayed the highest antiplasmodial activity with IC_{50} value of 0.083 μM, while three of the HEDICIN derivatives (**61b-d**) were also among the most active antiplasmodial, with IC_{50} below 2 μM [50]. Sashidhara and co-workers evaluated novel keto-enamine chalcone-chloroquine based hybrids (**63**) against CQ-S (3D7) of *P. falciparum*. Some of the compounds displayed comparable antimalarial activity with chloroquine. Compounds with high *in vitro* antimalarial activity were evaluated for their *in vivo* efficacy in Swiss mice against P. *yoelii*. Compounds **63a-b** showed an *in vivo* suppression of 99.9% parasitaemia on day 4 [51]. In similar manner, Sashidhara group has explored new chloroquine-chalcone based hybrids (**64**) and tested against 3D7 and K1 strains, respectively. Significant activity was observed by most of the compounds in resistant strains as compared to chloroquine. Among, compound **64a** displayed promising *in vitro* activity against K1 strain with an IC_{50} value of 82.93 nM [52]. David and co-workers synthesized a set of 4-aminoquinoline-chalcone amides (**65**). These compounds were screened against the CQ-S (3D7) and CQ-R

(W2) strains of *P. falciparum*. All compounds were found active, with IC_{50} values ranging between 0.04-0.5 μM and 0.07-1.8 μM against 3D7 and W2, respectively. Amide (**65a**) found to be most active as potent as CQ against 3D7, while it displayed a two-fold higher activity than CQ against the W2 strain [53].

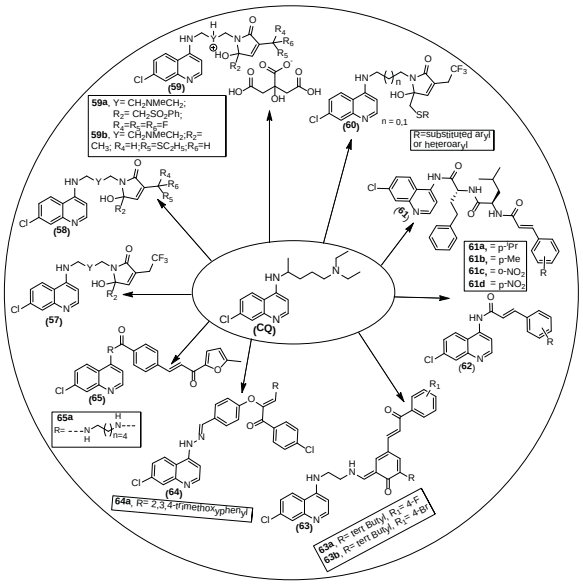


Figure 1.1.8 - Variations at the side chain of chloroquine having γ-hydroxy-γ-lactams, chalcones, chalcone-amides.

Sharma *et al*. [54] investigated new quinolinyl chalcones (**66**) and quinolinyl pyrimidine (**67**) molecules. Synthesized compounds were tested against *P. falciparum in vitro*. Chalcone derivatives did not show significant antimalarial activity. Among the quinolinyl pyrimidines, compounds having a 4-oxo linkage between the quinoline and the pyrimidine ring were inactive whereas, 4-amino linkage between quinolinyl pyrimidines (**67a-d**) displayed antimalarial activity with MIC ranging from 1 to 2 μg/mL. Sunduru *et al*. [55] synthesized novel 4-aminoquinolines by incorporating oxalamide (**68**) and triazine (**69**) functionalities in the side chain and studied their SAR. These deravites were evaluated for their *in vitro* antimalarial activities against CQ-S strain of *P. falciparum*. Compounds **68a-c** and **69a-c** with potent *in vitro* antimalarial activity and good SI values were also evaluated for their *in vivo* activity against the CQ resistant N-67 strain of *P. yoelii* in Swiss mice at 50 mg/kg/day for 4 days by intraperitoneal route (ip) and found to be not significantly active as compared to CQ. Singh and colleagues explored β-lactam-4-aminoquinoline conjugates having urea (**70**) and oxalamide (**71**) linkers by the use of alkyl chain length along with their antimalarial activities. The compounds with urea tethered series showed IC_{50} ranging from 42.38 nM to 193.15 nM. According to SAR, the compounds with longer alkyl chain length (n=6) demonstrated better antiplasmodial activity compared to their short alkyl chain counter parts. Compound **70a** was found to be the best molecule with an IC_{50} value of 42.38 nM. The oxalamide linker series showed IC_{50} ranging from 34.97 nM to 120.65 nM. Among the tested compounds, compound **71a** was most active and displayed an IC_{50} of 34.97 nM [56]. A series of 4-aminoquinoline-triazine conjugates (**72**) were synthesized and evaluated for their *in vitro* antimalarial activity against CQ-S and CQ-R strains of *P. falciparum* by Manohar *et al*.[57] In order to identify the potent molecules, various substituents were introduced at second and fourth positions of the triazine nucleus. Compounds **72a-d** exhibited promising antimalarial activity against both CQ-S (D6) and CQ-R strains (W2) with IC_{50} ranging from 0.21 to 0.48 μM. Several analogues did not show any cytotoxicity up to a high concentration (48 μM) other compounds exhibited mild toxicities but the selectivity index for antimalarial activity was high for most of these conjugates.

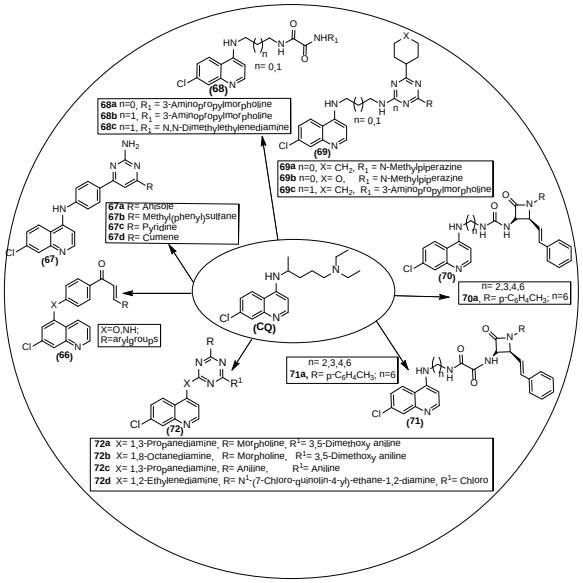


Figure 1.1.9 - Variations at the side chain of chloroquine having chalcones, pyrimidine, oxalamide, triazine, urea motifs.

Singh and co-workers discovered pyrimidine-5-carboxylates (**73**) linked covalently to 4-aminoquinoline nucleus and evaluated for their antiplasmodial activity against both CQ-S and CQ-R strains of *P. falciparum*. These analogues displayed activity in the nanomolar range; particularly compound **73a** exhibited lowest IC_{50} value of 153 nM against CQ-R strain [58]. Recently, the same research group explored the synthesis of prototype **74** and systematic evaluation of structure-activity relationships of series of potent quinoline-pyrimidine based molecules. In this investigation, among the 18 compounds tested, five compounds displayed IC_{50} values in the range of 22-70 nM against D10 strain. One compound did not show considerable activity, and the remaining compounds had IC_{50} values ranging between 113 and 4310 nM. In particular, compound **74a** was found to be active against both Dd2 (IC_{50} 43 nM) as well as D10 (IC_{50} 22.6 nM) strains [59]. Manohar and colleagues examined various derivatives by connecting 4-aminoquinoline and pyrimidine entities (**75**) together via flexible linear chain diaminoalkane linkers [60]. All the tested compounds showing IC_{50} against CQ-S in the ranging from 0.006-0.44 μM, and against CQ-R strain IC_{50} in the range from 0.016-1.24 μM. Based on the *in vitro* potency, compounds **75a-b** selected for *in vivo* acivity. The compounds were administered to the *P. berghei* infected mice model through oral route of administration. Both compounds exhibited excellent *in vivo* antimalarial activity without any toxicity. The compound **75a** was better active as compared to **75b** and CQ. Treatment with compound **75a** at three doses of 30 mg/kg, produced almost complete suppression of parasitemia and cured 80% of the treated mice, as compared to only 20% cured by compound **75b**. To resolute, the effect of different heterocyclic rings linked to the 4-aminoquinoline nucleus, Casagrande and group synthesized series of 7-chloro-N-(heteroaryl)-methyl-4-aminoquinoline (**76-78**) and 7-chloro-N-(heteroaryl)-4-aminoquinoline (**79**) and tested *in vitro* against CQ-S (D-10) and CQ-R (W-2) strains of *P. falciparum*. All tested compounds exhibited from moderate to high activity against the CQ-S (D-10) strain, with IC_{50} ranging from 5.50 to 399 nM (CQ IC_{50} was 14.3 nM). Only two compounds **79a-b** showed very low activity against D-10 strain with IC_{50} in the range 2656 nM and 1858 nM, respectively. Ten compounds exhibited a strong activity against CQ-R (W-2) strain, resulting from 4.8 to 16.4 fold active than CQ with IC_{50} values as low as 20.9 to 60 nM compared to 317.1 nM of CQ. Six compounds were found to be 1.7 to 4.2 fold more active than the reference drug. The most interesting compounds are the arylimidazolyl derivative (**77a**) the N-methylimidazolyl derivative (**78a**) and the thienyl derivative (**79c)** which are associated with a very strong antiplasmodial activity [61]. Manohar *et. al.* [62] synthesized a new series (**80**) by systematic chemical modifications in the triazine moiety via suitable linkers to 4-amino-7-chloroquinolines, and all synthesized compounds **80a-e** were screened for their antimalarial activity. All the evaluated compounds displayed good activity

against CQ-S strain IC_{50} ranging from 0.09-0.67 μM, whereas, in the case of CQ-R strain IC_{50} ranging from 0.11-2.06 μM. Compounds **80a-e** was found to be significantly more active than CQ against CQ-R (W2) strain of *P. falciparum*. Compounds having amino alcohol side chain with the free terminal hydroxy group enhances the activity of compounds towards both the strains of *P. falciparum*. Another important finding has been observed with improved antimalarial activity for compounds containing aromatic substitution on 1,3,5-triazine than their aliphatic counterparts. This may be attributed to greater lipophilic character associated with aromatic compounds.

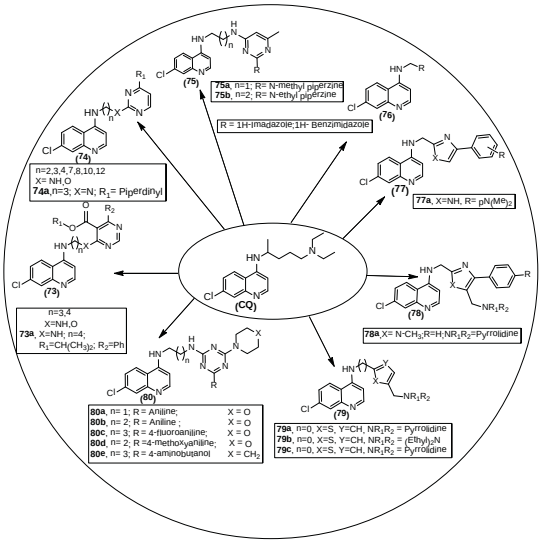


Figure 1.1.10 - Variations at the side chain of chloroquine having pyrimidine, imadazoles, triazine, motifs.

Kumar *et al.* [63] investigated 4-anilinoquinoline triazines (**81** and **82**) and evaluated *in vitro* for their antimalarial activity against CQ-S (3D7) strain of *P. falciparum*. Compounds **81a-c** and **82a-b** displayed the superior antimalarial potency IC_{50} values ranging from 3.01 nM to 7.03 nM to CQ. Based on *in vitro* efficacy and β-hematin inhibitory activity formation, compounds **81a-g** and **82a-c** selected for *in vivo* activity evaluation. Compounds **81d-e** were found to be orally active at a dose of 100 mg/kg x 4days against CQ-R strain of *P. yoelii*. In similar manner, Bhat and colleagues synthesized set of molecules **83** obtained from 4-aminoquinoline and substituted 1,3,5-triazines. Subsequently, all the synthesized compounds were tested for antimalarial screening against CQ-S (3D-7) and CQ-R (RKL-2) strains of *P. falciparum* and found that compounds **83a-b** were more potent molecules, whereas, compounds **83c-d** exhibited enhanced activity in case of mutant strains [64]. Opsenica group synthesized 4,7-ACQ-based antimalarial agents (**84** and **85**) that are also efficacious BoNT/A LC inhibitors. Synthesized compounds evaluated against three *P. falciparum* strains, CQ-S (D6), CQ-R (W2), and MDR (TM91C235) respectively. Several compounds exhibited potent activity against the CQ-S strain, compounds **84a-f** and **85a** being more potent than CQ (IC_{50}<9 nM). In addition, all derivatives are more active against the CQ-R strain than CQ. Furthermore, all compounds are also more active than CQ against the MDR TM91C235 strain. Compound **84a** is very active against the CQ-S strain having IC_{50} value of 6.41 nM, and found to be 60 and 30 times more potent than CQ against the CQ-R strain and MDR strains, respectively. Moreover, it is interesting to note that **84e** is more than100 times active than CQ against the CQ-R strain, 3 times more potent than CQ against the CQ-S strain, and 38 times more active against the MDR C235 strain than CQ [65]. Kumar *et al*. [66] explored new 4-aminoquinolines by incorporating triazine moiety in the side chain (**86**). A series of 19 compounds were evaluated against CQ-S strain of *P. falciparum*. Among the tested compounds, compound **86a** found most potent molecule with IC_{50} value of 4.43 ng/mL. Compounds **86a-c** selected for *in vivo* activity against *P. yoelii* by i.p. route at a dose of 50 mg/kg/day. The compounds **86a-c** exhibited more than 99% suppression on day 4. Whereas, on day 6 compound **86a** showed 99.11% suppression.

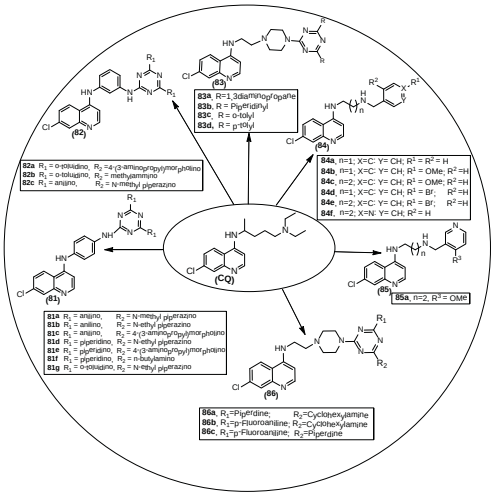


Figure 1.1.11 - Variations at the side chain of chloroquine having pyridine, pyrimidine, motifs.

Recently, the synthesis of 1,2,3-triazoles by a process known as Cu-mediated click chemistry was explored to combine different molecules affording new analogues of chloroquine. Manohar *et al.*[67] reported synthesis of a series of 4-amino-quinoline-1,2,3-triazole (**87**) and 4-aminoquinoline-1,2,3-triazole-1,3,5-triazine (**88**) derivatives and evaluated their antimalarial activity against D6 and W2 strains of *P. falciparum*. Analogues **87a-b** displayed 0.90, 0.59 µM, respectively. Derivatives **88a-e** exhibited antimalarial activity ranging from 0.58 to 0.98 µM. Like-wise, Pereira and co-workers synthesized 7-chloroquinolinotriazole derivatives (**89-91**). All compounds were evaluated for their *in vitro* activity against *P. falciparum*. Among twenty-seven derivatives; five of them displayed moderate antimalarial activity with IC_{50} values ranging from 9.6 to 40.9 µM [68]. Raj group synthesized a series of 1H-1,2,3-triazole-tethered isatin-7-chloroquinoline (**92**) and 3-hydroxy-indole-7-chloroquinoline (**93**) conjugates and evaluated for their antimalarial activity against CQ-R (W2) strain of *P. falciparum*. Conjugates **92** displayed activity ranging from 118 to 346 nM. Moreover, reduced conjugates **93** slightly improved activity compared to conjugates **92**. Among the tested conjugates compound **93a** found to be potent with an IC_{50} value of 69 nM [69].

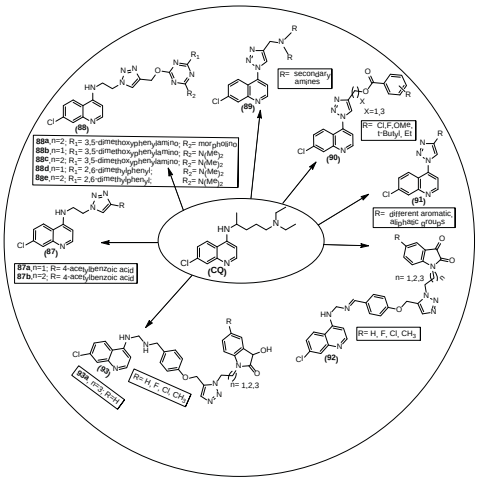


Figure 1.1.12 - Variations at the side chain of chloroquine having triazole, triazine, isatin,motifs.

Different strategies have been explored to construct the molecules with improved activity against drug-resistant *P. falciparum* and also with enhanced metabolic stability. Based on these postulations, Pandey *et al.*[70] introduced tetrazole moiety in the side chain of 4-aminoquinoline (**94**) and several derivatives **94a-i** were synthesized. All the tested compounds displayed moderate activity against the CQ-S (3D7) strain with IC_{50} values ranging from 10.66 to 216 nM, CQ-R strain with IC_{50} values ranging from 73.70 to >1023 nM, respectively. Compounds with high activity *in vitro* **94a-i** were selected for *in vivo* efficacy in Swiss mice model against CQ-R N-67 strain of *P. yoelli*. This was done by i.p route at the dose of 50mg/kg x 4 days, and survival of mice until day 28. Compounds **94a-b** exhibited 99.99% parasitemia suppression on day 4, whereas, other compounds **94c-i** displayed suppressed parasitemia between 20.43% to 73.91%. Compounds **94a-b** with the promising result by i.p route were further screened at 100 mg/kg x

4days by oral route. Both compounds exhibited promising results with 99.99% parasite suppression on day 4, and 60% survival on day 28 of treatment. By using similar approach, Tukulula and co-workers synthesized a series **95** by incorporating bulkier substituents such as aromatic and tetrazole rings at lateral part while varying the length of the alkyl side chain to circumvent metabolic N-dealkylation and evaluated for antiplasmodial activity against both strains of *P. falciparum.* Compounds **95a-f** were more active than CQ on all the tested *P. falciparum* strains, particularly against the CQ-R (K1) strain. Compound **95d** was found to be exhibiting 36 fold greater activity having IC_{50} value of 1.0 nM. Based on *in vitro* activity, *in vitro* ADME characterization of the selected compounds **95b-d** was assessed. The solubility of these selected compounds was generally poorer than that of CQ diphosphate. Compound **95c** was selected for *in vivo* antimalarial efficacy evaluation against *P. berghei* ANKA infected male C57/BL6 mice. This compound was administered orally at four different concentrations (20, 10, 5, and 1 mg/kg dose) once a day for four days. Compound **95c** at 5 mg/kg exhibited 47% reduction in parasitemia on day 7 [71].

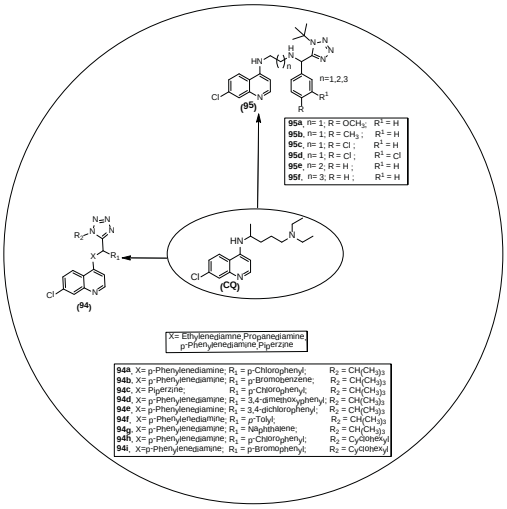


Figure 1.1.13 - Variations at the side chain of chloroquine having tetrazole motifs.

1.3 Conclusions

The emergence and spread of resistance against conventional antimalarial drugs has put enormous pressure on public health systems to introduce new chemotherapeutic agents. During the last few years, considerable progress has been made by various research groups to renovate the side chain of CQ and develop new promising antimalarial agents. As discussed above, development of 4-aminoquinolines (4-AQs) with better pharmacological efficacy, especially against CQ-R parasites have mostly depended on the extensive derivatization approaches. By taking into account, the importance of basicity of quinoline ring and side chain pendant nitrogen atoms for antimalarial activity of 4-AQs, many research groups have synthesized promising analogues having different basic moieties *viz* piperazine, isoquinuclidine, triazine, guanidine and triazole in the side chain. Also, systematic variation of the side chain length and the introduction of thiazolidine, thiourea, amides, tetrazole and bulky substituents led to enhance antimalarial activity. Overall, most of the compounds displayed promising *in virto* against CQ-R strains. Whereas, in the case of *in vivo* antimalarial activity, compounds displayed significant suppression rate but failed at curative indicator. In order to afford best molecules careful derivatization approaches followed by better understanding of the structure-activity relationships and biotransformation mechanisms involved in toxicity and resistance can provide additional quinoline analogues effective against CQ-R strains with better chemotherapeutic and reduced toxicological profiles.

Acknowledgments

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