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Review Article

Recent Updates in chemistry of quinoline analogs as potential antimalarial agent with utilization of Chem3D software

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Abstract

Plasmodium parasites, which cause the fever sickness known as malaria, are passed from infected female Anopheles mosquitoes to people through mosquito bites. Several parasite species, including P. vivax, P. falciparum, P. malaria, P. ovale, and P. knowlesi, are liable for human malaria. P. falciparum and P. vivax are the two most hazardous strains. The most pervasive and lethal malaria parasite on the continent of Africa is P. falciparum. In most nations outside of Sub-Saharan Africa, P. vivax is the most prevalent malaria parasite. The earliest symptoms of malaria, including fever, headaches, and chills, appear 10 to 15 days after an infected mosquito bite. These symptoms might be mild and difficult to identify from other infections. If untreated, P. falciparum malaria can progress to severe illness and death in less than 24 hours. By 2020, malaria will impact over half of the world's population. People with low immunity moving to regions with high malaria transmission, such as migrant workers, mobile populations, and travelers, are at a significantly higher risk of contracting malaria and developing severe disease. These individuals also include infants, young children, pregnant women, HIV/AIDS patients, and others. In this review we have utilized Chem3D software to visualized the 3D structure of Quinoline ring with its electronic structure which have provided numerous information regarding the stability of the quinoline scaffold. Additionally, we studied different marketed drug using this software and found its IC50 value against the several strains of the malaria causing agent. And we provided whole statistics regarding the severity of strain and better activity of the drug against the strain which will be helpful for the scientists to find out the better treatment for the malaria. We place these findings in an chronological context and suggested new options for identifying pharmacological targets and transmission- blocking techniques

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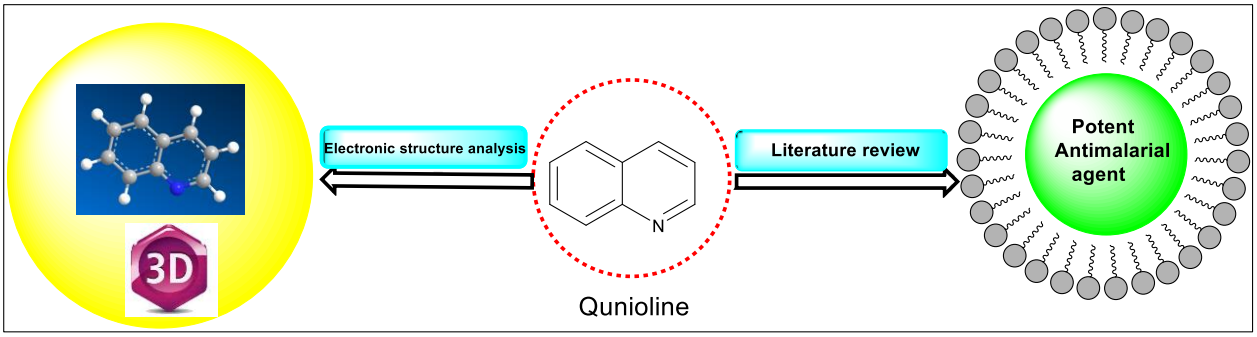
Graphical Abstract:



1.1 Pathophysiology of Malaria.

Both parasite- and host-related factors affect the pathogenicity of malaria. The most deadly form of malaria is P. falciparum, and the severity of infection caused by various Plasmodium species varies.1,2 It has pathogenic traits like sequestration (attachment of infected red blood cells containing trophozoites to endothelial cells of the microcirculation of different organs to avoid splenic removal), cytoadherence (mature forms of parasites like asexual stage and gametocytes attach themselves to vascular endothelium of different organs like the liver, lungs, heart, and brain, as well as subcutaneous adipose tissues and placenta.3

Periodic fever, chills, shivering, headache, nausea, vomiting, and various other clinical symptoms are typically linked with malaria infections. However, P. falciparum is also known to cause serious illnesses such severe anemia, respiratory distress, cerebral malaria, and other organ failure. For a very long time, it was thought that P. vivax infections were somewhat benign, produced only modest clinical signs, and that the parasites did not hide in the deep capillaries of the organs. Recent research, however, has raised the prospect of parasite sequestration in organs, as shown by the severe diseases and fatalities linked to P. vivax infection. Immediately following the initial liver stage infection that transitions to the blood infection, in which merozoite forms of the parasite attack red blood cells (RBCs), clinical symptoms of malarial infections begin.4

In difficult cases of malaria, worldwide, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) have been observed. Deep breathing, respiratory distress, pulmonary edema, airway blockage, damaged alveoli, reduced gas exchange, and an increase in pulmonary activity are all symptoms of this illness.

1.2 Life Cycle of Malaria

The life cycle of malarial parasite involves two hosts and three cycles as shown in Figure 1. The female Anopheles mosquito takes a blood meal and inoculates sporozoites which infect the liver cells and stay there until they mature into schizonts (Exo-erythrocytic cycle). After rupturing, the schizonts release merozoites which enter the bloodstream and infect the RBCs (Erythrocytic cycle)5

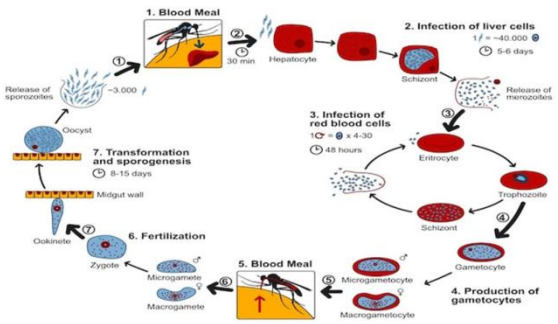


Figure 1: Life cycle of Malaria

The sexual cycle begins when a tiny number of asexual parasites commit to generating sexual progeny, known as gametocytes. Mature gametocytes can circulate in human blood for days, increasing their chances of transmission to the mosquitoes. A few minutes after entering the mosquito midgut, both male and female gametocytes use proteases to depart the RBCs and develop into eight microgametes and one macrogamete, which combine to form the zygote6. The zygote develops into a motile ookinete that passes the epithelial layer of the midgut wall to create an oocyst. In the oocyst, parasites go into their third cycle of asexual replication, creating thousands of sporozoites that go out into the hemolymph. Sporozoites attach to the mosquito's salivary glands and infect the gland, where they remain until they are given to a new vertebrate host via a mosquito bite, so resuming the cycle.6

2. Treatment of Malaria

2.1 Drugs being used for the treatment of malaria

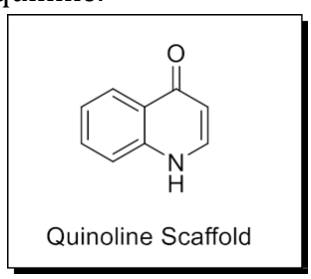
The medications used to treat malaria target distinct phases of the parasite's life cycle, allowing the disease to be controlled at different levels. Antimalarial medications are frequently used to treat malaria target distinct phases of the parasite's life cycle, allowing the disease to be controlled at different levels. Antimalarial medications are frequently used in combination to attack many stages of the life cycle at the same time, increasing therapeutic efficacy while reducing treatment time. Because of its great efficacy, low cost, and manageable side effects, chloroquine (CQ) has remained the antimalarial medicine of choice.

Most antimalarial medications derived from natural products, such as artemisinin and quinine derivatives, have been shown to be quite effective.

Chemical classification of the antimalarial drugs is as follows:

- Quinoline Derivatives
- Artemisia Derivatives
- Amino alcohol
- Sulphonamide and Sulfone Derivative
- Antifolate
- Antibiotics
- Other drugs

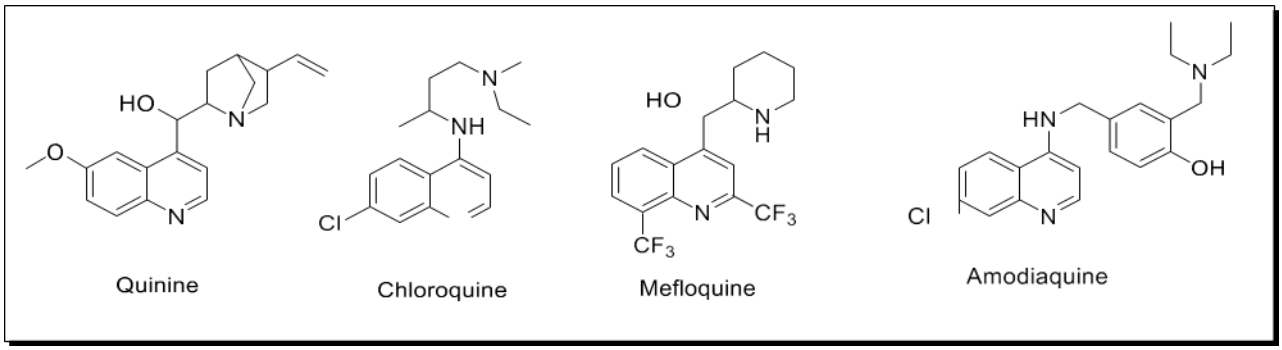
1) Quinoline derivatives-Quinolines are synthetic compounds with the skeleton of 4-oxo-1,4-dihydroquinoline, also known as the tautomeric 4-hydroxyquinoline. Quinine, extracted from the bark of Cinchona calisaya, was the first semisynthetic derivative of quinine, while Chloroquine was the first semisynthetic derivative of quinine.[7]



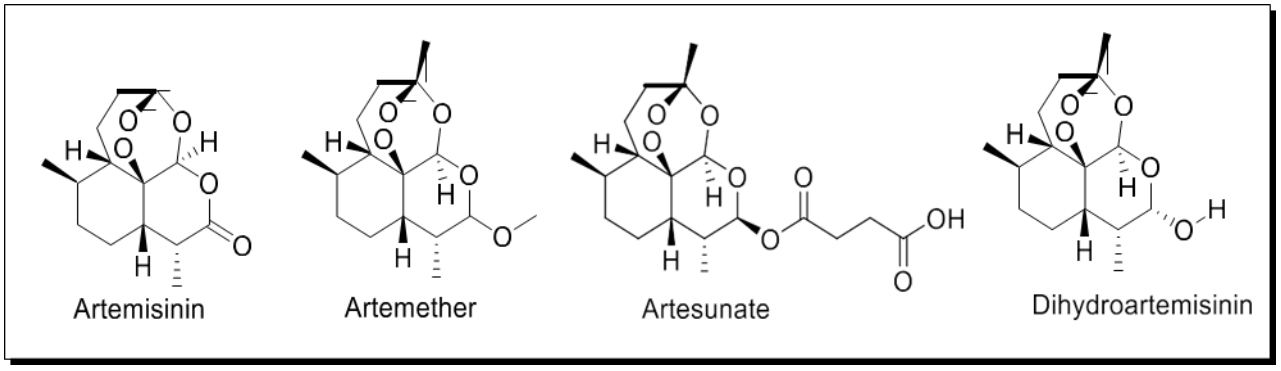
Quinoline Scaffold

Quinoline derivative antimalarial agent consists of-

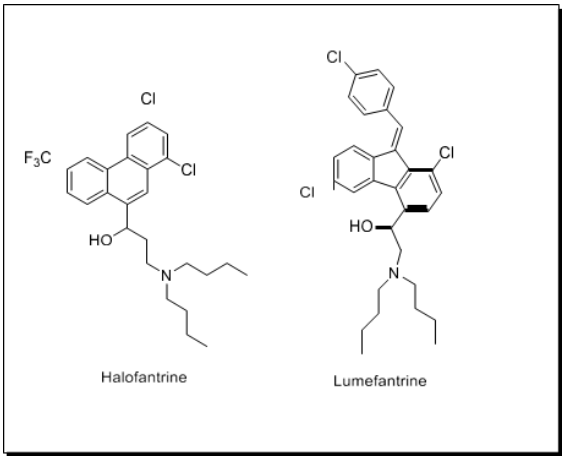
- Cinchona alkaloid- Quinine, Quinidine
- 4-Aminoquinolines- Chloroquine, Amodiaquine, Piperaquine
- 8- Aminoquinolines- Primaquine, Bulaquine



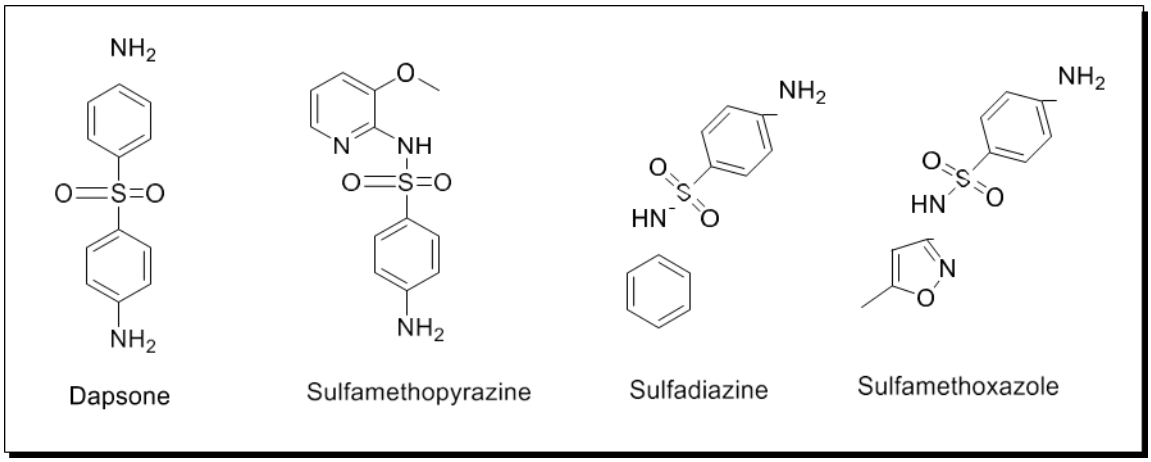
Artemisia Derivatives -After being extracted from Artemisia annua plants, artemisinin is very easily improved by crystallization, but it is quite challenging to synthesize artemisinin from scratch. Antimalarial activity of the sesquiterpene lactone artemisinin is closely related to a peculiar endoperoxide trioxane moiety.[8]



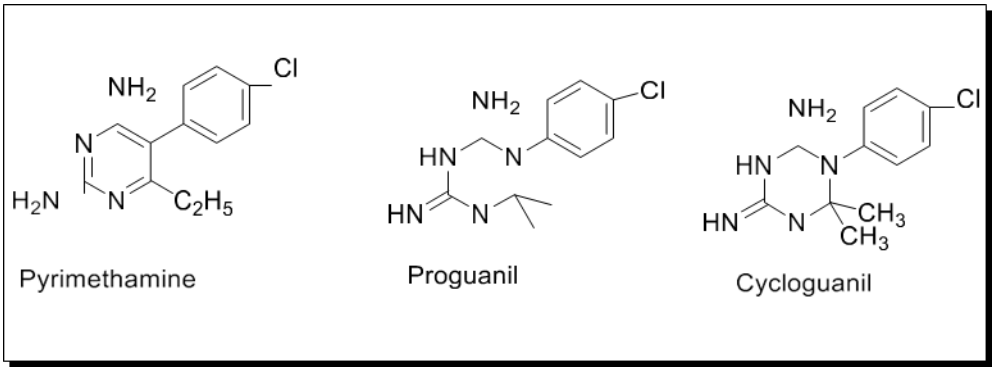
2) Amino Alcohol Orally administered antimalarial drugs include amino alcohols like halofantrine and lumefantrine. These drugs function as blood schizonticides, killing both chloroquine-sensitive and chloroquine-resistant plasmodia during the erythrocytic phase of the parasite life cycle. In dose-finding and non-comparative clinical trials, the effectiveness of halofantrine in the treatment of P. vivax malaria and falciparum malaria in regions with chloroquine- and sulfonamide/pyrimethamine-resistant malaria has been demonstrated.



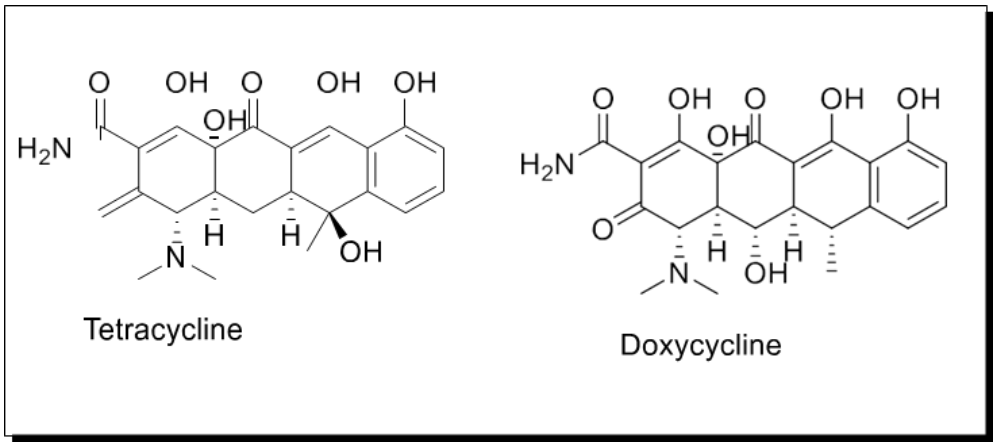
1) Sulphonamide and Sulfone derivatives- Sulfonamides and sulfone are effective in preventing placental malaria thereby improving maternal and fetal birth outcomes. The ability of a number of sulfonamides chalcone derivatives to suppress β-hematin production in vitro and their efficacy against cultured P. falciparum parasites were studied.[9]



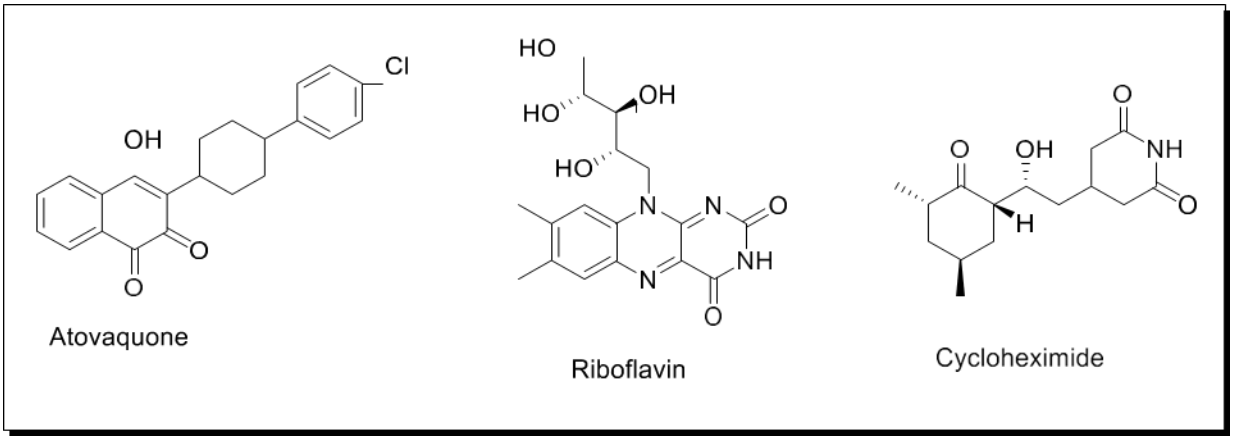
2) Antifolate - Dihydrofolate reductase (DHFR) is inhibited by antifolate antimalarials like pyrimethamine and cycloguanil, depriving the parasite of vital folate cofactors. Within P. falciparum.



3) Antibiotics:



4) Other drugs –



2.1 Mechanism of action of currently available drugs

The pre-erythrocytic, erythrocytic, and exo-erythrocytic stages of the life cycle are the targets of contemporary antimalarial drugs. Based on how they work, they are separated into three groups:

Aryl amino alcohol compounds (fast Schizonticidal drugs): quinine, quinidine, halofantrine, lumefantrine, chloroquine, amodiaquine, mefloquine, cycloquine etc.Artemisinin compounds: artemisinin, dihydroartemisinin, artesunate, artemether, arteether etc.11

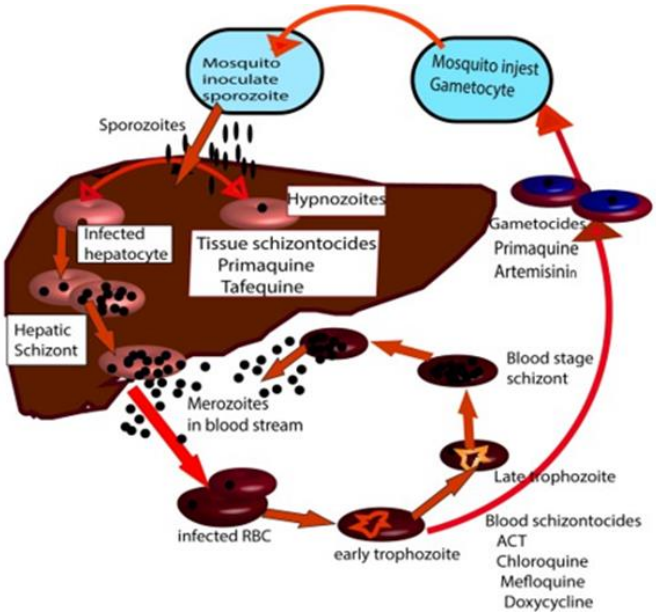


Figure 2: Mechanism of action of current drugs

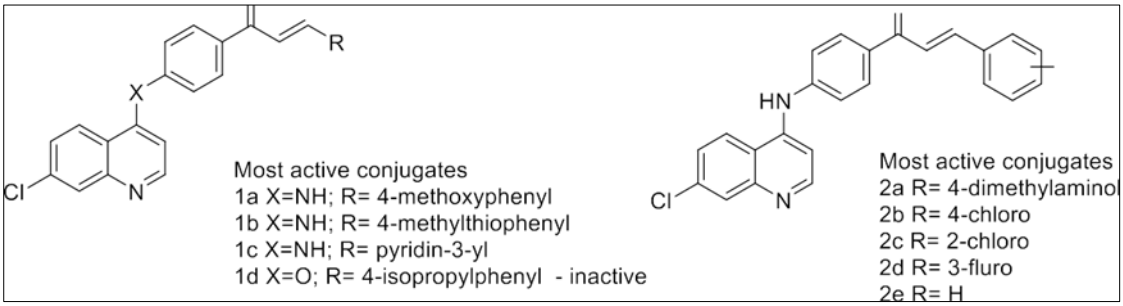
Scizonticidal medications either attack the parasite's sexual erythrocytic stages (blood schizonticides) or the dormant stage (hypnozoites) (tissue schizonticides). Gametocidal medications like primaquine and quinine kill the parasite's sexual erythrocytic forms, preventing gamete transmission to mosquitos and hence the cycle's completion. Sporonticides like primaquine and proguanil prevent malaria from spreading to healthy people by inhibiting the production of malarial oocytes and sporozoites in infected mosquitos. Many of the medications are schizonticidal.12 However, no widely used medicine was designed using a totally logical approach with the goal inhibiting known targets. As a result, the capacity of most antimalarial drugs to inhibit a specific

target is still unknown. Additionally, because to mutations or gene duplication in transporter or enzyme genes, the parasite has become increasingly resistant to well-known treatments. For instance, mutations in pfmdr1 and pfcrt lead to chloroquine resistance. Point mutations in dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) are the root cause of antifolate resistance. Due to a point mutation in the P. falciparum kelch-like gene, even the most potent antimalarial medicine artemisinin and its derivatives may become ineffective against P. falciparum. Artemisinin medications use this protein as a major marker. As a result of the rapid spread of malaria and the emergence of resistance to existing antimalarial medications, it is critical to create novel chemicals that can be used as potential antimalarial agents.13

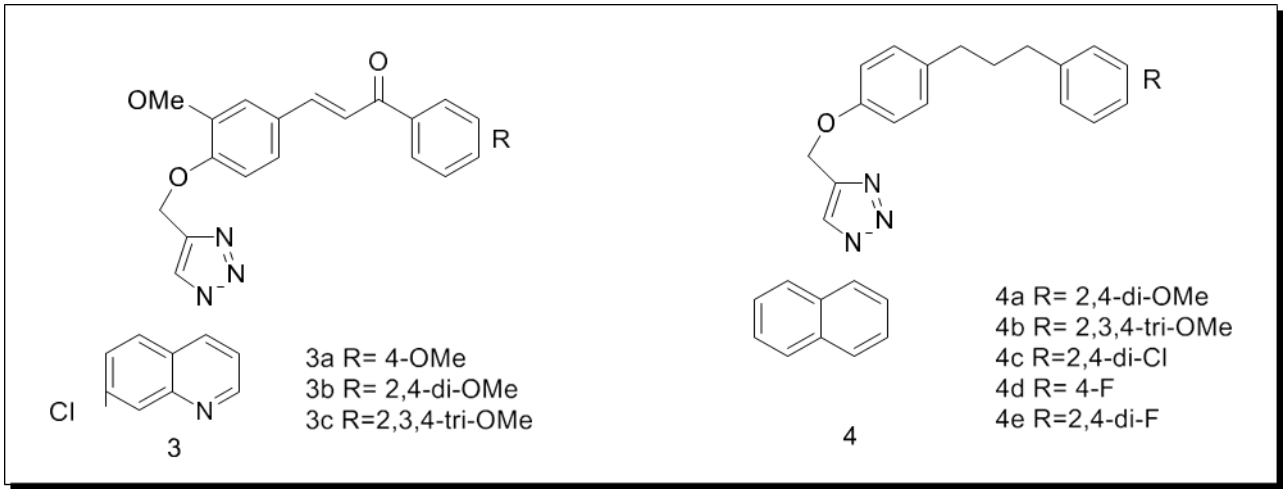
3. Quinoline Class of Drugs

3.1 Background Study

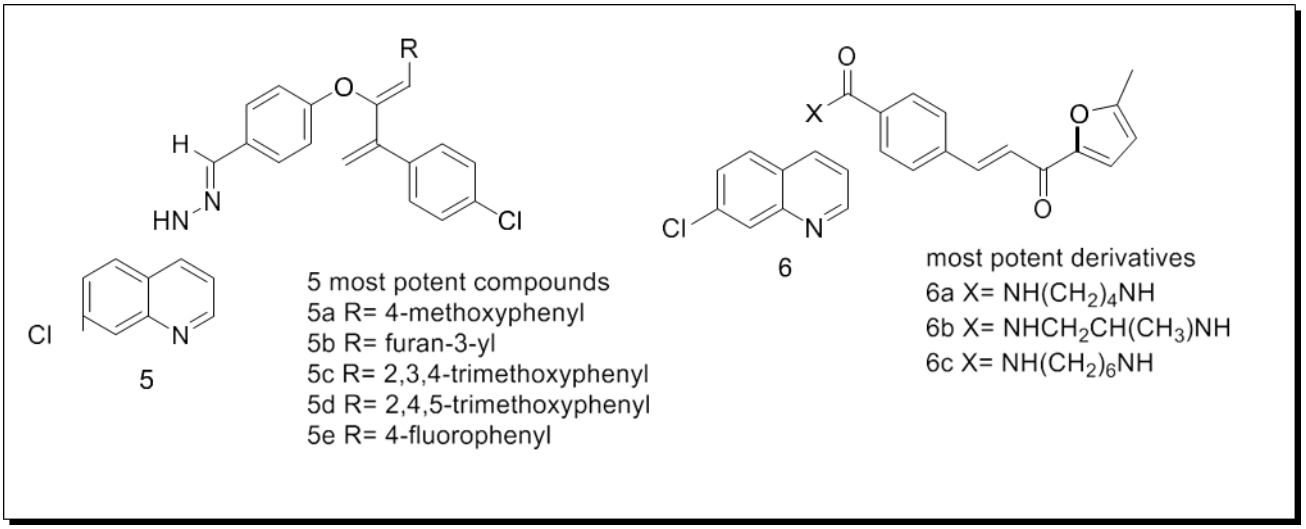
Due to its simplicity, low or minimal host toxicity, economical synthesis, and superior clinical effectiveness, quinoline continues to be a desirable moiety for the design and synthesis of novel compounds with increased antimalarial activity. 4- and 8- aminoquinolines, such as Primaquine and Chloroquine, were created as a result of the modification to the quinoline scaffold.



Compounds 1a-c and 2a-e differ in the R group attached to B-ring of chalcone. The amino linked compounds were found to show very mild activity against CQS NF54 strain of P. falciparum. Quinoline-chalcone hybrids linked via oxo and amino linkages (1a-d). 2a-e are hybrids formed by amine linkage between quinoline and chalcone.



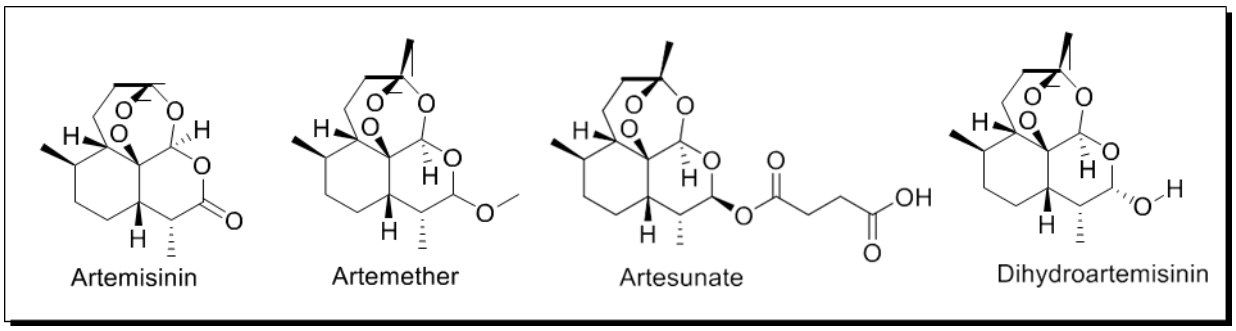
Out of all the above compounds (Figure 4), 3b-c and 4b showed sub micromolar potency and 3b was found to be most active with IC50 values of 40, 70 and 90 nM against D10, Dd2 and W2 strain of P. falciparum, respectively.



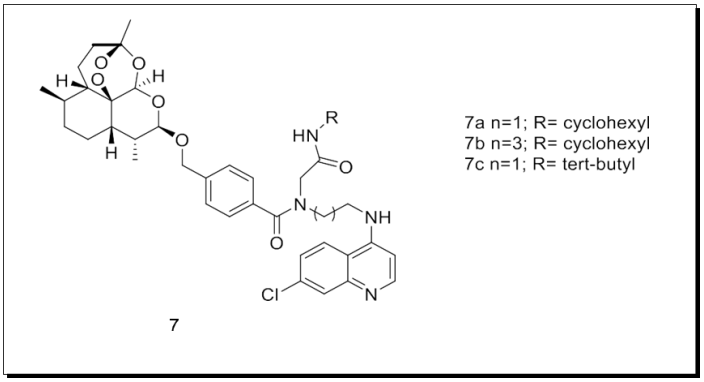
Compounds 6a-c were found to be potent against the CQS (3D7) strain of P. falciparum with IC50 values between 30 and 300 nM (IC50 of CQ= 463 nM) and even more potent against the CQR(K1) strain with IC50 values of 80 and 315 nM. However, by connecting the two moieties by amide group (compounds 6a-c) resulted into loss of antimalarial activity against the resistant strain.14

Artemisinin-quinoline hybrids:

Artemisinin kills all species of plasmodium that infect humans. In vitro P. falciparum IC50 values (median and range) have been reported as 4.2(0.5–34.6), 4.3(0.5–23.2), and 16.2(1.3–58.3) nM for artesunate, dihydroartemisinin, and artemether respectively.



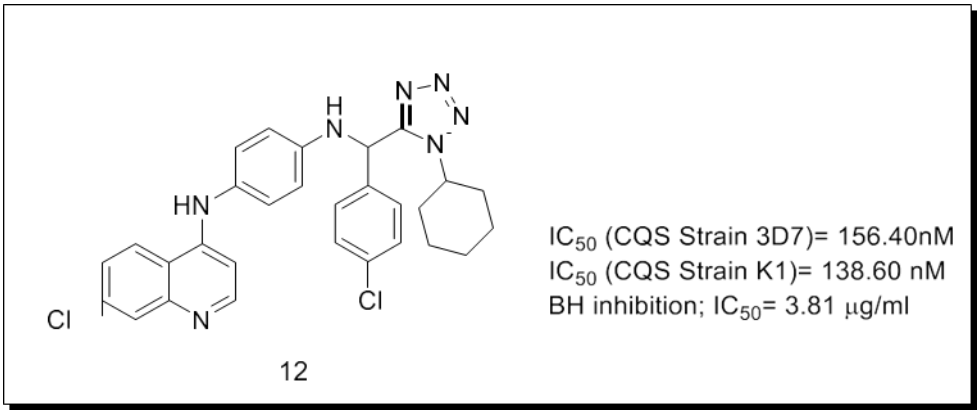
The hybrids 7a-c showed in-vitro anti plasmodial activities with IC50 values between 19 and 23 nM as compared to chloroquine (IC50= 20 nM). This showed that activity of the hybrid compounds was Comparable to chloroquine against CQS D10 strain of P. falciparum while being more potent against CQR K1 strain of P. falciparum with IC50 values of 19-23 nM and 219 nM respectively.15



The aldehyde was then subjected to reductive amination with various alkyl aminoquinolines to form derivatives 8a-d. Oxidation of the alcohol to carboxylic acid followed by treatment with oxalyl chloride and 4-(3- aminopropyl amino)-quinoline resulted in the formation of derivative 9. All the hybrids showed good activity against CQS (3D7) strain of P. falciparum (5-22 nM) and excellent activity against CQR (K1) strain (8-16 nM) as compared to chloroquine (16 and 187 nM, respectively) while it was comparable with artemisinin (11 and 9 nM, respectively).

3.1.2 Sulphonamide quinolone derivatives

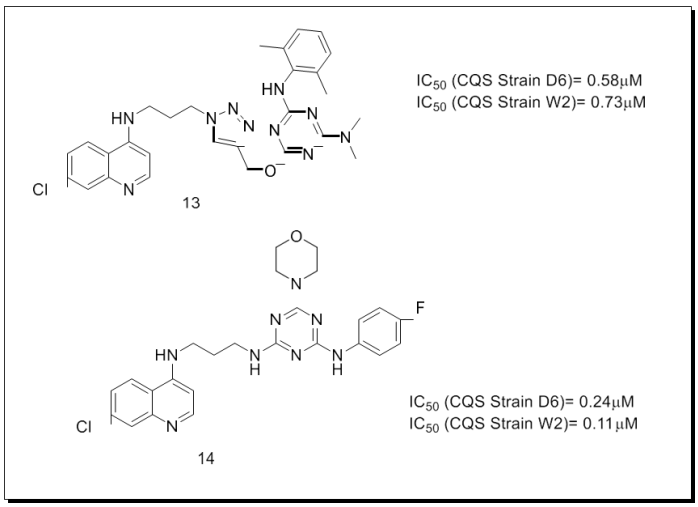
There have been reports of quinoline-sulfonamide hybrid compounds as potential antimalarial medications. These compounds have different linker groups attaching aryl sulfonamide moieties to the aminoquinoline molecule. They exhibit effective antimalarial activity, functioning by preventing parasite growth without compromising the integrity of the membrane surrounding the red blood cell.16 Compound 12 shows good antimalarial activity their IC50 values are 0.10 and 0.2



12

3.1.3 Heterocyclic derivatives of 4-aminoquinoline

Chloroquine-tetrazole conjugates were developed because it was observed that the tetrazole moiety is able to coordinate with the iron center in the heme.17 The compounds synthesized (Figure 10) were found to show promising antimalarial activity against both sensitive and resistant strains of P. falciparum.The above compounds (Figure 11) showed good antimalarial activity against the sensitive and resistant. strain with the most active compound being 14 as compared to CQ (CQS strain D6: IC50= 0.05 μM; CQR strain W2: IC50= 0.43 μM). It can also be observed that adding a triazole moiety between CQ and triazine resulted into decrease in the antimalarial activity as shown by compound.18



3.1.4 Ferrocenyl derivatives of 4-aminoquinoline

The above compounds were tested against both CQS (D10) and CQR (D2d and KR10) strains of P. falciparum and it was observed that series 15a-e and 16a showed greater activity than 17a-e against CQS strain, although lesser than ferroquine. But compounds 17a-e show greater activity against the CQR strains. This was evaluated based on RI (resistance index) which ranged from 0.5 to 24.7. It was observed that greater the RI, greater is the loss of antimalarial activity against the CQR strains. The disubstituted CQ-ferrocenyl compounds had the lowest RI which indicated their higher activity against the resistant strains as compared to the CQS strain of P. falciparum.19

3.2 Structure-activity relationship

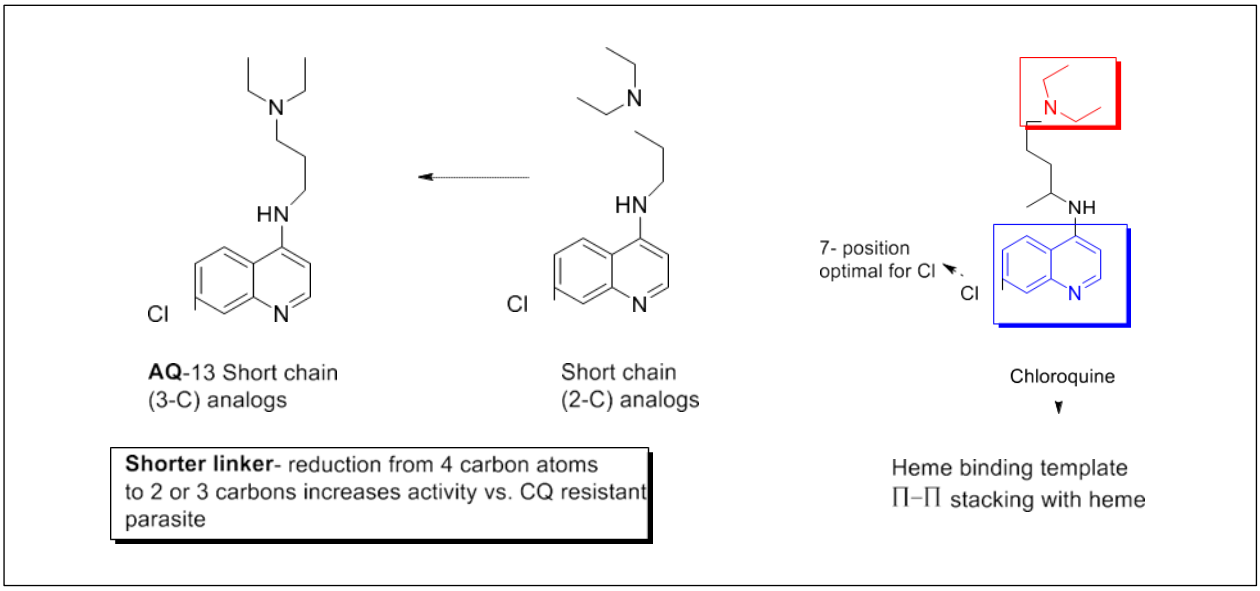


Figure 13: - Structure Activity Relationship of 4-Aminoquinoline

A series of analogues with different dialkylamino side chains at the 4-position. Compounds with dialkylamino chain lengths of less than four or higher than seven were shown to be efficacious against CQ-sensitive, CQ-resistant, and multidrug-resistant P. falciparum strains, with IC50 value of 40-60 nM against the K1 resistant strain. However, in shorter chain counterparts like AQ-13, N-dealkylation may occur, lowering lipophilicity and increasing cross resistance up to and beyond CQ.

4. Recent statical data of malaria cases:

We analysed statistical data of malaria from 2010- 2021. Malaria deaths reduced by 74%, from about 35 000 in 2000 to 9000 in 2019. The number of estimated deaths has remained the same for the past 3 years. The malaria mortality rate reduced by 81%, from 2.7 to 0.5 per 100 000 population at risk in year between 2000 and 2021. India accounted for about 83% of all malaria deaths in 2021. Between 2020 and 2021, all countries in this South-East Asia region in which malaria deaths occurred had reported either a reduction or no change in the malaria mortality rate except for Myanmar, where the mortality rate increased more than three times, from 0.2 to 0.74 per 100 000 population at risk. In the countries like Bhutan and Timor-Leste have reported zero malaria deaths since 2013 and 2015, respectively. Thailand reported zero indigenous deaths for the first time and Nepal reported one death in year 2021.20

4.1 Recent malaria cases in South-East Asia region from (2010-2021)

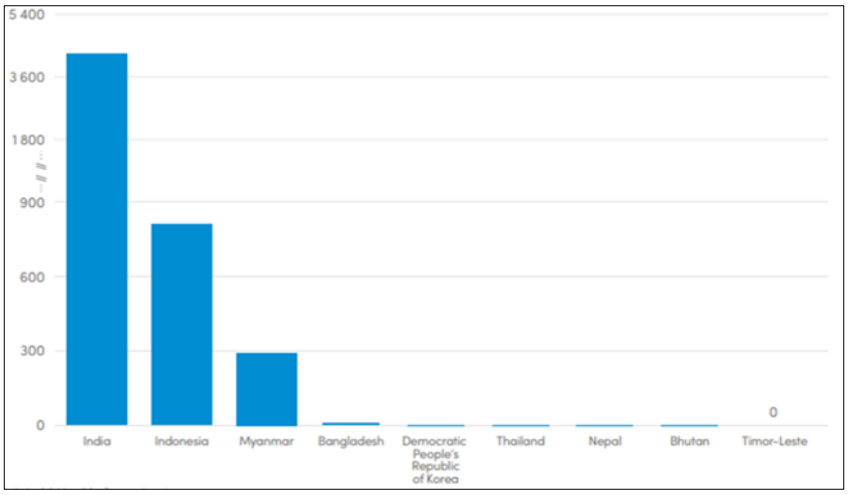


Figure-2. Recent malaria cases in South-East Asia region from (2010-2021)

4.2 Recent malaria cases in India

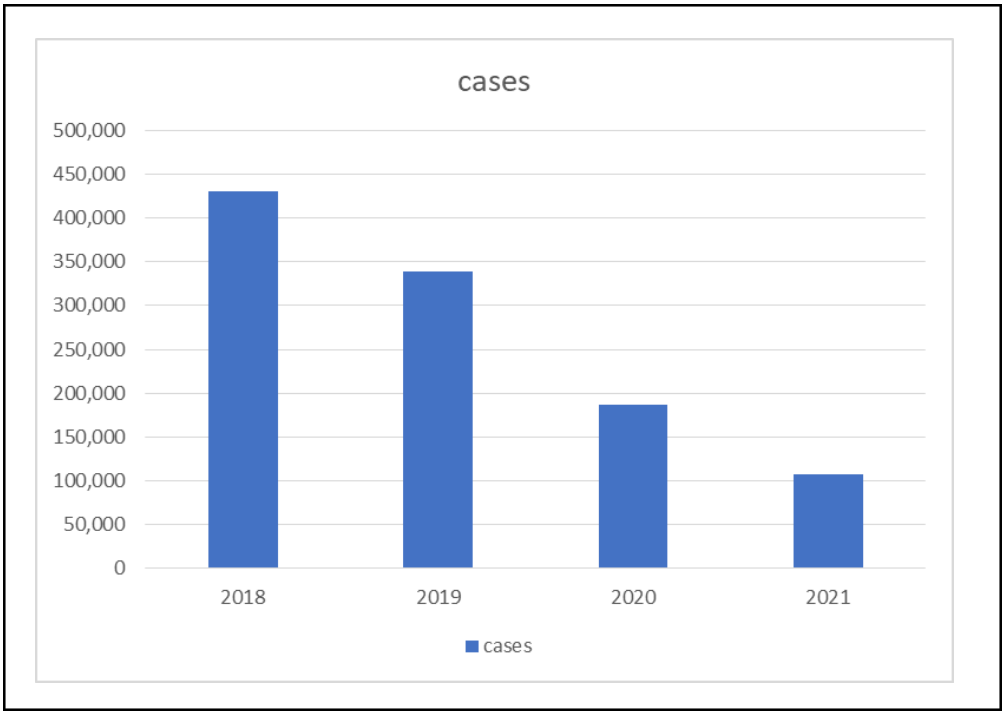


Figure-3. Recent malaria cases in India

5. Recent updates of heterocycles as anti-malarial drug discovery ring potential-

5.1 Aminoquinolines-

• Bhat et al discovered Chloroquine-sensitive (3D-7) and chloroquine-resistant (RKL-2) strains of P. falciparum these were used as test subjects for the in vitro antimalarial activity of a series of hybrid 4-aminoquinoline1,3,5-triazine derivatives.17

• A number of 4-amino-7-chloroquinolines with dibenzyl methylamine (dibemethin) side chains were created by Zishiri and colleagues. These substances were discovered to be equally effective against cultures of P. falciparum that was chloroquine-sensitive and chloroquine-resistant.21

5.2 Fused Pyran-

• McCracken et al. created a variety of 4-methoxy-6-styryl-pyran-2-ones, dihydro analogues, and derivatives of photo-dimers, both natural and synthetic. These were tested for their ability to combat P. falciparum malaria. In comparison to the conventional medications, the compound had the most potent anti-malarial action.22

• Kalaria and his coworkers have developed a novel combinatorial library of fused pyran derivatives under microwave irradiation, by using a one-pot, three-component reaction of 5-(1H-imidazole-1-yl)-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde with various active methylene compounds and enolizable ketones/phenols in the presence of piperidine as a basic catalyst. The in vitro antibacterial, antituberculosis, and antimalarial activities of each drug was examined.

5.3 Indole-

• Lebar et al. created analogs of 3-pyrimidylindole and then tested them for cytotoxic, antimalarial, and central nervous system effects. The strongest antimalarial drug has a high IC50 value for the P. falciparum strain.

• Teguh et al created a novel class of antimalarial drugs based on indol-3-yl connected to the 2-position of a 4- aminoquinoline moiety. These molecules shown promise anti-P. falciparum action.21

5.4 Quinazoline and Quinoxaline-

• Verhaeghe et al. efficiently and conveniently synthesized a variety of unique quinazolines containing 4-thiophenoxy and 2-trichloromethyl groups, and they assessed the compounds' in vitro anti plasmodial capabilities. The series showed strong anti-K1-multiresistant P. falciparum strain action.22,23

5.5 Pyrimidine-

• Sharma et al. and colleagues created a number of substituted quinolinyl pyrimidines and chalcones. The substances were tested for their antimalarial and antitubercular effects on the NF-54 strain of P. falciparum as well as their in vitro antitubercular activity against Mycobacterium tuberculosis H37RV.24

• Novel pyrimidine derivatives were created by Dahlgren and his colleagues and their antimalarial activity was tested against the K1 strain of P. falciparum. It was said to be the highly active pyrimidine molecule.25

5.6 Pyrazoline-

• Under microwave irradiation, Karad et al. developed a number of novel morpholino quinoline-based conjugates containing pyrazoline moiety. The synthetic compounds were tested for their early in vitro antibacterial activity against a panel of pathogenic bacterial and fungal strains, antituberculosis activity against the Mycobacterium tuberculosis H37Rv strain, and antimalarial activity against P. falciparum. Compound demonstrated greater antimalarial potency than quinine, with an IC50 of 0.015 mM as opposed to 0.826 mM.26

5.7 Triazole-

• Nalmala Devender and colleagues created Novel b amino alcohol grafted 1,2,3-triazoles, who then tested them for antiplasmodial and antimalarial efficacy in vivo. Compounds had strong action

against the chloroquine-sensitive (Pf3D7) strain, with corresponding IC50 values of 0.87 and 0.3 mM.27

• Sandeep K. Dixit et al. produced triazole-based fluoroquinolone analogs by straightforward alkylation and click chemistry. Using ciprofloxacin as the gold standard, these analogs were assessed for their in vitro antimalarial activity against a chloroquine-sensitive strain of P. falciparum.28

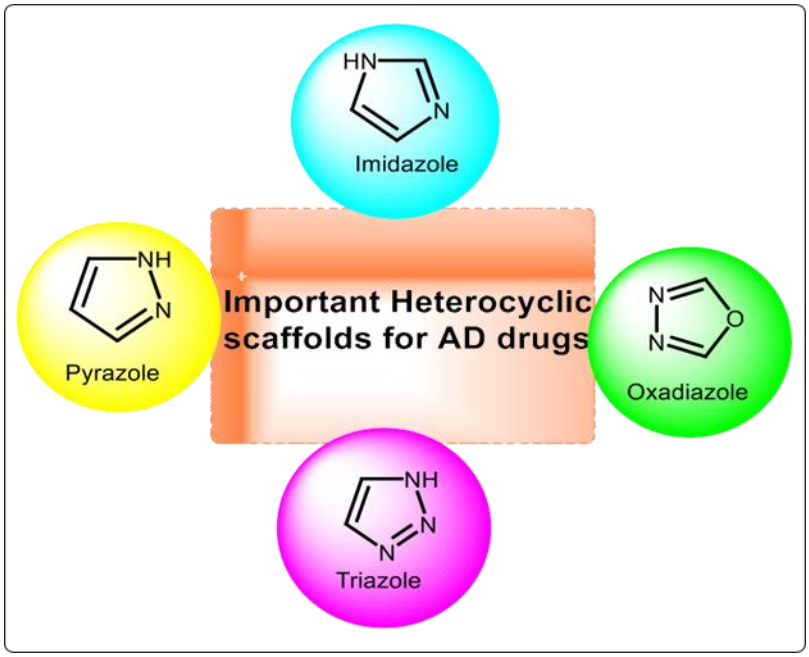
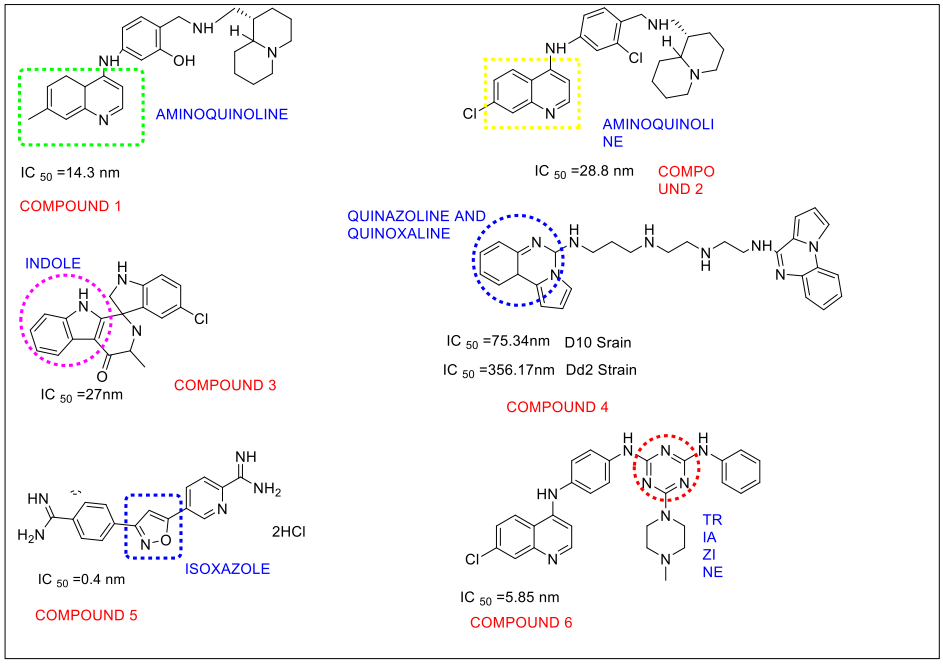


Figure 4. Importance of heterocyclic scaffolds for Antimalarial drug

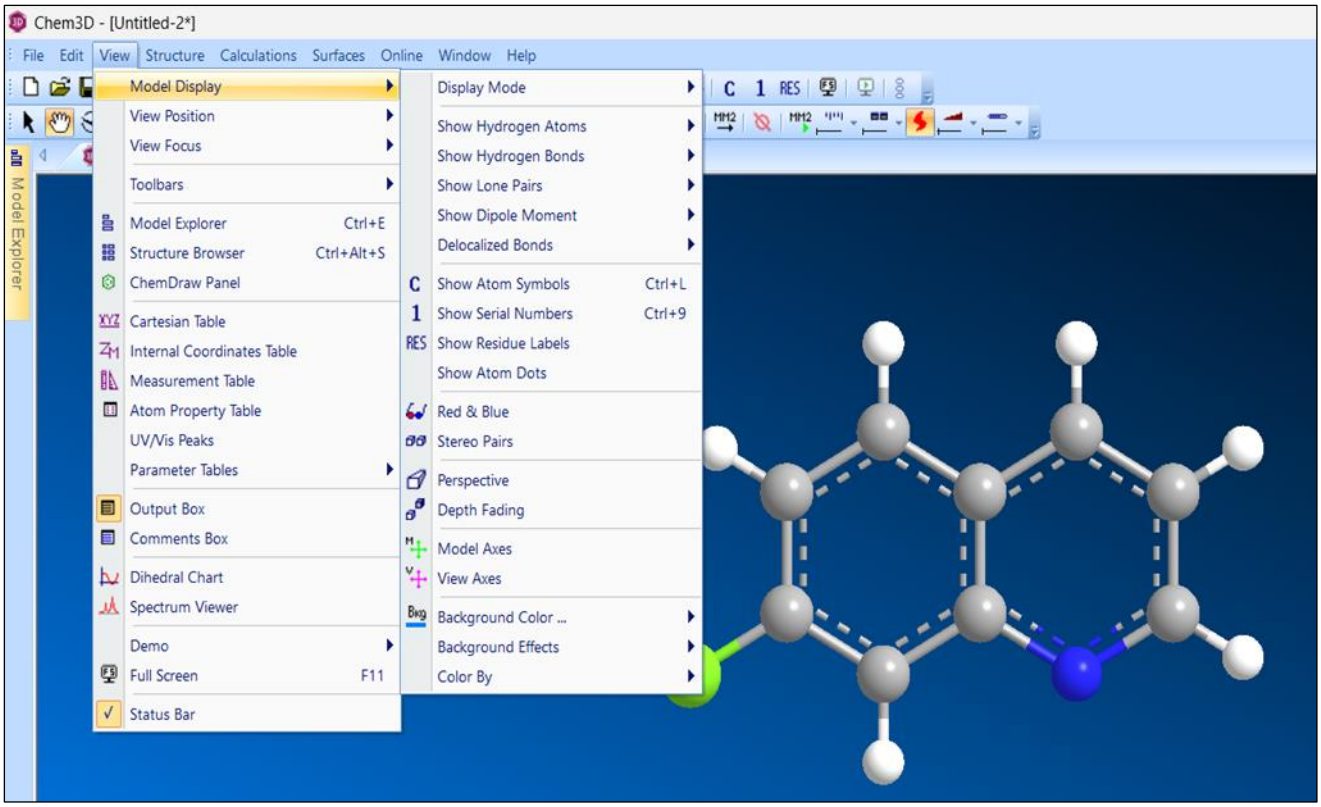
6. Analysis of several quinoline derivatives:

These molecules have been selected for further experimental view based on its IC50 value which were showed in the literature. We further analyzed these compounds using the chem3D software and found numerous novel properties.

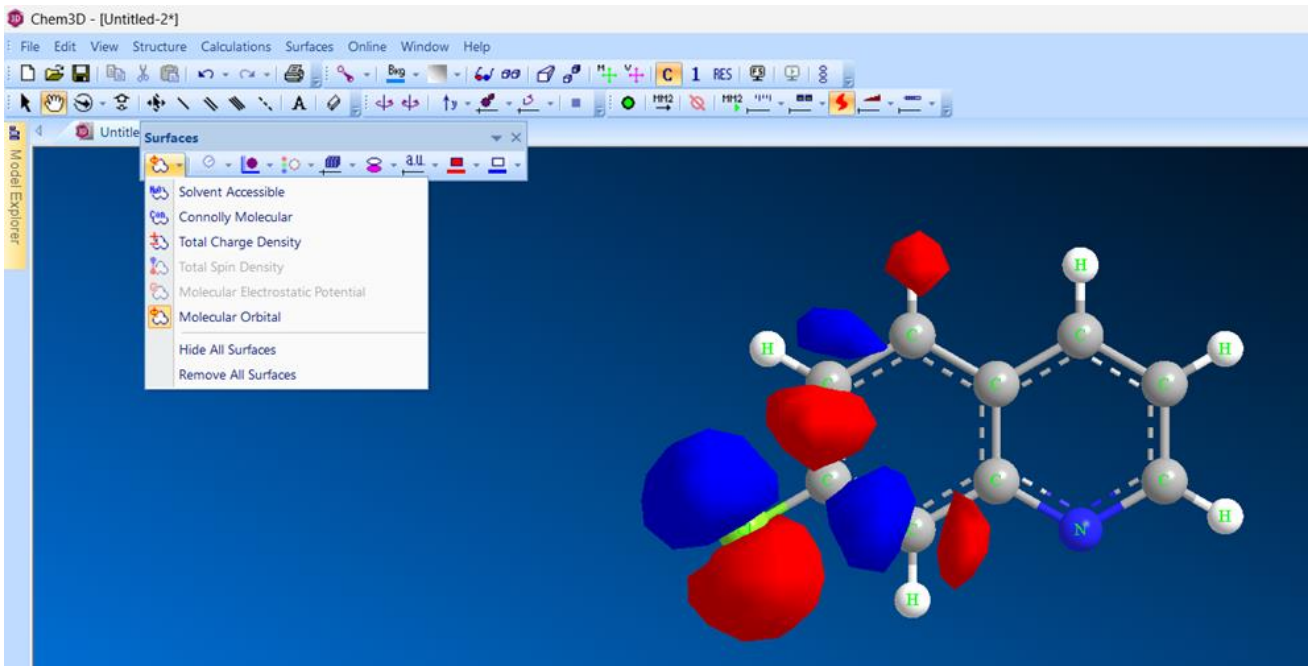


7. Experimental section:

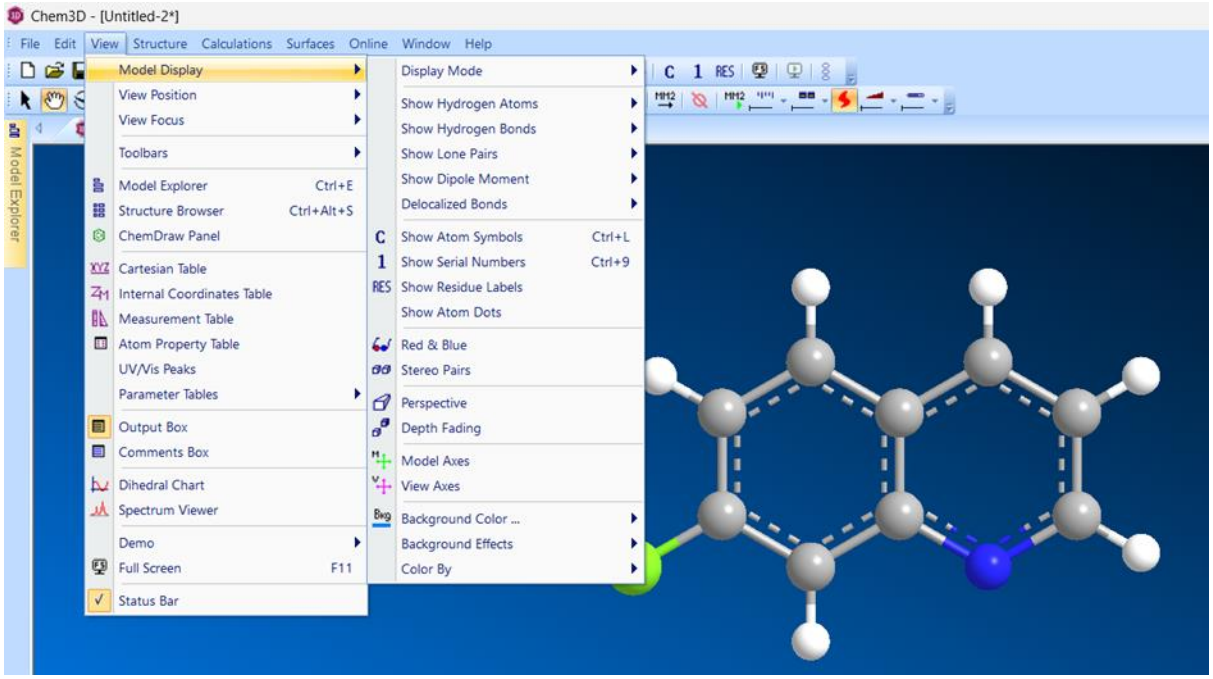
Step 1: Search molecule (Quinoline) on Chem 3D software:



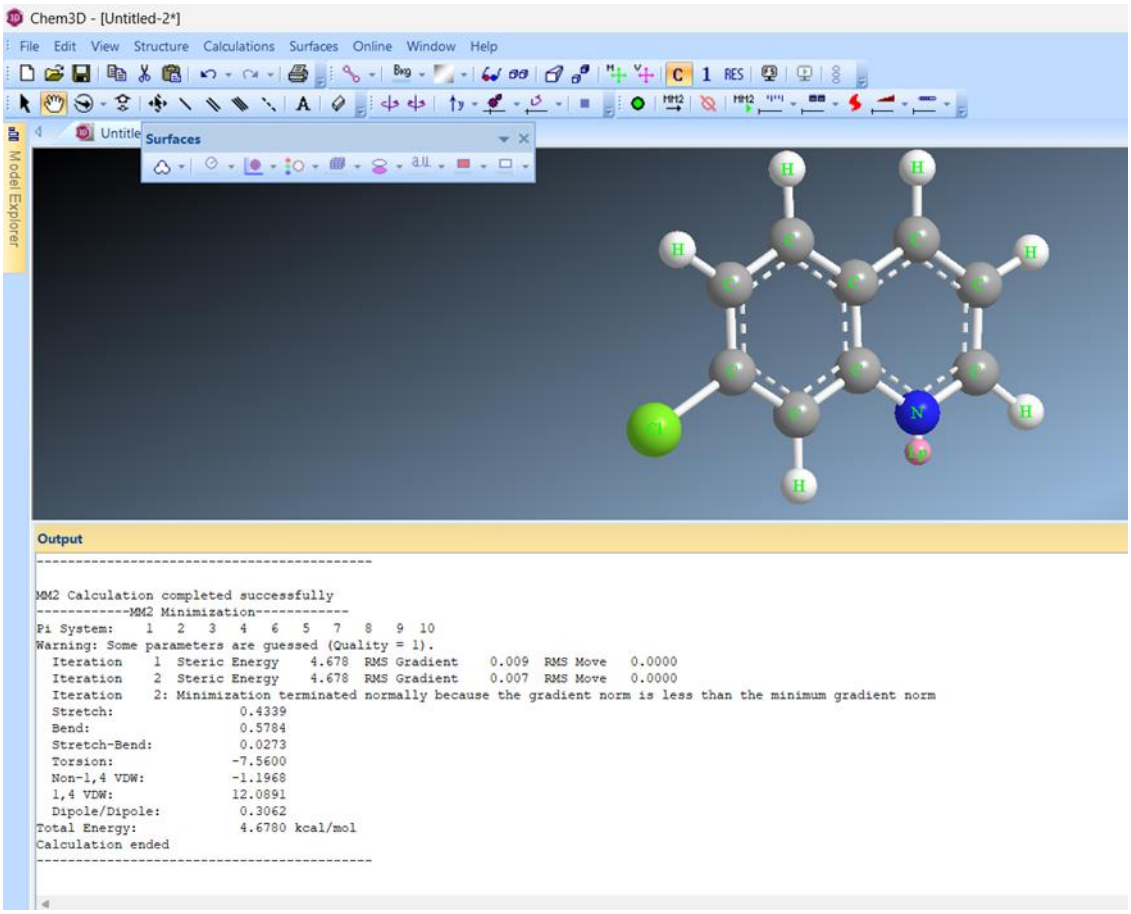
Step 2: Molecular orbital structure of compound using 3D Chem draw



Step 3: Calculations of molecule using Chem 3D software:



Step 4: Analysis of all the compounds after calculation:



Conclusion-

In this review, we performed quantum analysis of numerous quinoline analogs and we selected molecules who have better IC50 value against the strain of malaria causing agents. Moreover, we observed better interactions of quinoline scaffold with receptor by reviewing different literature. We analyzed 3D structure and electronic structure of all the derivatives using Chem 3D Software and gaussian software respectively. We reviewed all the data based on activity on quinoline ring against different malaria causing strains and found better drug molecule with an outstanding IC50 value. These molecules showed good activity which will be better information for the researchers to marked out the novel treatment for the malaria.

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CONFLICT OF INTEREST:

The author declares no conflict of interest, financial or otherwise.

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