International Journal of Academic Research and Development
ISSN: 2455-4197
Impact Factor: RJIF 5.22
www.academicjournal.in
Volume 3; Issue 6; November 2018; Page No. 281-285

Review on chemical synthesis and antimalarial activities of *Amopyroqunine*

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Abstract
Malaria is one of the major death causing problems for human in tropical and sub tropical area of the world largely in Africa. For these, scholars investigate antimalarial drug based on evaluating the risk of exposure to infection preventing mosquito bites giving as medical cure. Antimalarial drug act by distributing the polymerization and the detoxification by any of heme, thus killing the parasites with is own metabolic wastes. The main class of active schizonetocide is 4- aminoqunoline and 8-aminoqunoline. Quinine is isolated from cinchona bark replaced the cured preparation and continued to be the major antimalarial drug till 1942. The one which is grouped under 4-aminoquinine is Amopyroquanine.
Amopyroquanine is an anti-malarial compound chemically and functionally related to chloroquine (CQ). Currently, it is used (in combination with other antimalarial) as the first choice to treat complicated plasmodium faliciparim. malaria in some countries in Africa and south America this Amopyroquanine is one of anti-malarial drug synthesized industrially and less toxic compared to the other types of anti-malarial drugs for treatment of malaria.

Keywords: malaria, amopyroquanine, synthesis, antimalarial drug

1. Introduction
The actual word malaria comes from the French and which means ‘’bad air [1] malaria is a protozoa disease that occurs in most tropical and sub -tropical area of the world, it is a major problem in many parts of the country [1, 2]. It is estimated that over 40% of the world population is exposed to the risk of malaria at any one time and that there are an estimated 2 million death associated with the disease per year [3]. it is one of the most dreadful protozoal disease effect human beings. for this reason it is important to prevent the exposure of malaria. Prevention of malaria is based on evaluating the risk of exposure to infection, preventing mosquito bites since advice should be giving regarding medical cure called anti malaria derug [3, 4].
Anti malaria drug is chemotherapeutic agent which is used for the preventation and treatment of malaria and ant malaria drugs used for prevention of relapse of malaria [3, 4] the effectiveness of anti malarial drugs differs with different species of the parasite and with different stage life cycle [3].
In 1926 some of the anti malarial drugs have been introduced. The bark of cinchona tree, growing in peru, was introduced in the early 17th as a cure of malaria. Latter it was realized to be a specific remedy for malaria, quinine is isolated from cinchona bark replaced the cured preparation and continued to be the major antimalarial drug till 1942 [4-6] the one which is grouped under 4-aminoquinine is Amopyroquanine.
Amopyroquanine is an anti malarial compound chemically and functionally related to chloroquine (CQ). Currently, it is used (in combination with other antimalarial) as the first choice to treat complicated plasmodium falciparum malaria in some countries in Africa and south America this Amopyroquanine is one of anti-malarial drug synthesized industrially and less toxic compared to the other types of anti-malarial drugs for treatment of malaria [7, 8].
This paper will explain anti-malarial drugs, current available antimalarial drugs, synthesis of Amopyroquanine, mechanism and mode of action of Amopyroquanine, metabolic stability and identification of Amopyroquanine, Amopyroquanine next-generation candidates in clinical development, application of Amopyroquanine, adverse effect of Amopyroquanine and including the concluding part of the paper.

2. Antimalarial drugs and current availability
2.1 Antimalarial Drugs
Malaria continuous to be the world diseases burden which 300 to 500million new cases and as many as million child hood death each year, because of the lack of indigenous drug, only about 1000 new cases are reported each year in the united states with immigration [9].
The treatment and prophylaxis for malaria has changed significantly with the evaluation of drug resistant organisms, much of the world now has chloroqunine resistant plasmodium falciparum regulating very difficult strategies for chemoprophylaxis and treatment than years past. The reduced availabilities of quinine and the luck of availabilities in the world some agents such as the artemisnin derivatives, including artesunate arthemetr, further limit the choice [10]. As

result of resistance, fixed combination of drug therapy has become more common [11]. The potential for toxicity is now more likely to be seen from these newer drugs because the older drug are begging used less frequently and those are less available for accidental or purposeful over dosing. Little toxicological data exists on many of these newer drugs particularly in combination over doses. Extension and enhancement of theraptic side effect profiles are frequently all that has been reported to date.

The classification of agents used as an antimalarial drug includes quinoline derivatives, dihydrofolate; reeducate inhibiters, artemisinin derivatives ubiqunone analog. Most antimalarial prisoners are the result of accidental child hood exposures or inteional adolescent and adult suicide attempts. Quinine hydroxychloroquinine and chloroqunine are quinine derivatives known to cause severe toxicity in over dose. The antimalarial quinine is an alkaloid derived from the bark of cinchona tree [7]. Quinine has been used as an antimalarial adulterant for street cocaine herein, a mesule relaxant and it is found in small amount in tonic water [1].

2.2 Currently available antimalarial drug analogues

In most cause antimalarial drug are targeted against the asexual erythrocyte stage of the parasite. The parasite degrades hemoglobin in its acidic food vacuole, producing free hem able to react with molecular oxygen and thus to generate reactive oxygen species as toxic by product. Major path way of detoxification heme moieties is polymerization as malaria pigment. Antimalarial drug act by distributing the polymerization and the detoxification by any of heme, thuse killing the parasites with is own metabolic wastes. The main class of active schizonetocide is 4- aminoqunoline, aryl alcohol including quinoline alcohol, antifolat compounds

Which inhibit the synthesis of parasitic pyriminidnes. The newest class of antimalarial drug is based on the natural endo peroxide artemisinin and its hemi Synthetic derivatives and synthetic analogue [7]. Also the other class 8-aminoqunoline is currently available antimalarial drug; moreover the classification is based on the chemical group and each individual to discussed bellow.

2.2.1) 4-Aminoquinolines

4-aminoquinine is a form of aminoqunoline with the amino group at the 4- position of the quinoline (fig.1). Verities of derivatives of 4-aminoquinoline are antimalarial agent useful in treating entocytic infections [12]. The main antimalarial is 4-aminoquinoline because they have proven to be the most highly successful class of compounds for the treatment and prophylaxes of malaria. They are easily synthesized, cheap and generally well tolerated. This compound as well as the qunoline alcohol is active against the intra-erythrocyte stage of the parasite.

The 4-aminoqunoline is able to accumulate to high concentration within the acid food vacuole of plasmodium to kill the parasite, example Amopyroquanine, chloroquine and amodiquine [13]. these 4-AQ exhibits tyrosine –kinas activity.

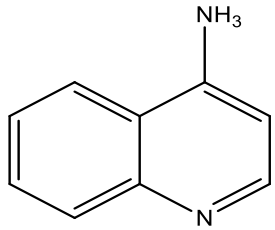


Fig 1: Structure of 4- aminoquinoline

4-aminoqunoline containing antimalarial drug such as, chloroquine, quinine and Amopyroqunine are mainstay of chemotherapy against malaria. The molecular base of the action of this drug is not completely understood, but they are the light to interfere with hemoglobin in digestion in the blood stage of the malaria life sycle. The high intera vascular choroquine concentration is proposed is to interfere with the polymerization heme. The presence of quinoline ring in the structure of quinine and impacrine as well as theraphtic properties of aminoquinoline where the logical precursor of further studies in antimalarial compounds and those with the basic dialkylaminoalkyl side chain in the 4-postion showed some promise. Chloroquine proved to be the most effective and least toxic among the previously known before amopyroquine is synthesized. All of the clinically useful drugs of these serious have the Chloro substitute at position 7, which seems connected with their specific antiplasmodial action. Amodiquine another member of these group has structural formula in which an aniline group replaces the alkyl amino side chain. It was synthesized by Burckhalter, *et al*. Its manner of antimalarial action is equal to that of chloroquine on strains of P. falciparum resistant to chloroquine. Amodiquine base is less bitter than its salts and this is of interest in pediatric practices [15].

There are well over 200 derivatives of 4- aminoquinoline with varying antimalarial activity, among these sontoquine less toxic than chloroquine but also less active than some others. Hydroxychloroquine has a lower chronic toxicity but all of them, including cycloquine have little advantage over chloroquine. French chemist produced varation on the chloroquine side chain with the intention of extending the durationof the schizontocidal effect [16].

2.2.2) 8- Aminoquinoline

These types of qunoline is a form of amino quinine with an amino group at the 8-position of quinoline. The 8-aininoquinoline family of drugs contains three members; primaquine, tafenoquine and pamaquine are used in the treatment of malaria. They may be used to eradicate malaria hypothesis from the liver and have both been used for malarial prophylaxis. The 8-aniinoquinoline drugs must not be given to patients, because they cause potentially fatal henaolysis in these patients. Pamaquine is no longer available a very where but primaquine is stillused routinely worldwide as part of the treatment of plasmodium vivax and plasmodiuni ovale malaria. Tafenoqtiine is currently clinical trials and

is not yet available to prescribed' 7. The compounds may produce adverse side effects such as pain and hemoglobin anemia and these, together with the need for frequent dosage, limit their value as prophylactic agents (i.e. as sporontocidal agents). A single dose of primaquine given to the host totally inhibits thesaprogenic malarial cycle in the vector [18].

The 8-anainoquinoline where the first group of compound to be synthesized, specifically for potential antimalarial activity. Initially attempts were made to incorporate diethyl amino alkyl amino side chain, which had been shown to enhance the activity of methyl blue, in to 6-metoxy quinoline moiety of quinine. In 1940, a large research program was in initiated in the united state of America, to develop more potent and less toxic antimalarial drugs. Froni these program, three compounds pentaquine, isopentaquine and primaquine were selected for further study. Primaquine proved to be the most satisfactory compound. Many analogs of the 8-aminoquinolines have been assessed for their antimalarial activities, but few have been more effective than primaquine. The difference of the drugs that grouped under 8-aminoquinoline is in the substituent(R) as shown below (Fig.2), including the table that shows the value of the substituent.

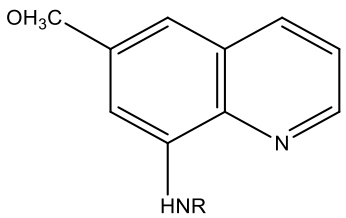


Fig 2: Stracture of 8-aminoqunoline

Table 1: Classifications of 8-aminoquino1ine

Drtig	R
Pamaquine	CH(CH3)(CH,) N(C; H5)2
Primaquine	CH(CH2)(CH2)3NHz
Isopentaquine	CH(CH)(CH2)3NHCH(CH3)z
Plasniocid	(CH) NH(CiH5)2
Pentaquine	(CH2)5NHCH(CH 3)›
Quinocide	(CH2) CH(CH3)NH

The earlier efforts the developments of 8-aminoquimoline analogs have been directed to extensive derivatization programs. This has lead to discovery of tafenoquine for prophylaxis against malaria infection and sitamaquine with utility for treatment of visceral leishnianiasies. Blaquine, primaquine pro-drug, has shown reduced met lieinoglobin toxicity and better malaria transmission blocking activity than primaquine. Better understanding of the mechanism of toxicity and efficiency may help in development of 8-aminoquinoline analogue with superior therapeutic action, reduced toxicity and broader utility [20].

Moreover, this two analogue explained above is currently available and thus are the base for the synthesis of amopyroquine specifically it grouped under 4-aminoquinoline. since Amopyroquine is one the derivative of 4-amnoquinoline and it can be synthesized in the laboratory by following the appropriate prouder.

3. Synthesis of amopyroquanine

The synthesis of polysubstituted quinoline derivative is the focus of the large number of studies because of their wide range of biological applications. Polysubstituted quinolines particularly amopyroquine are very important compound for the treatment and control of malaria because of their medicinal application ". The anti-malarial drug amopyroquine might have been derived from equine as it has a quinoline nucleus it also has five functional group three amines (all different-one aromatic, one tertiary, and one secondary), a phenol and an aryl chloride. There are four rings, three aromatic and one saturated heterocyclic.

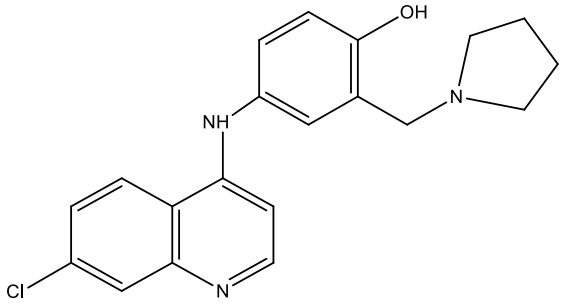
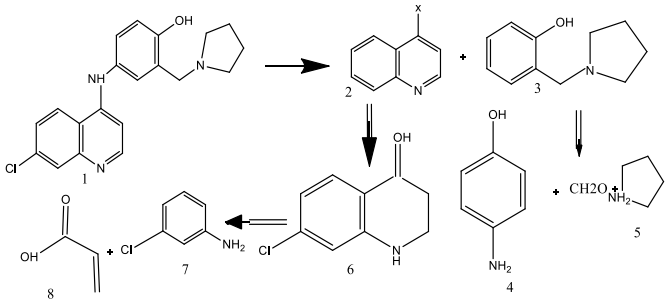


Fig 3: Structure of amopyroquanine

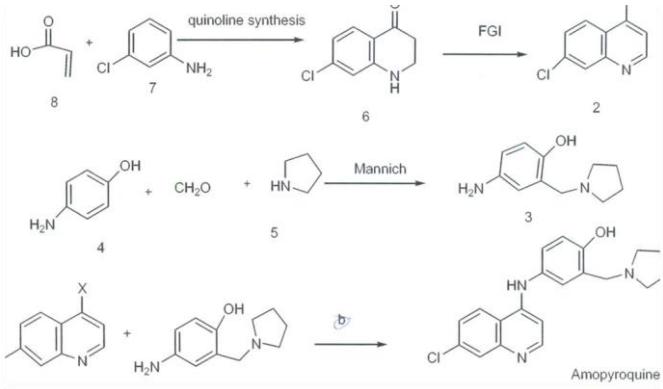
There are many possible disconnections or retro synthesis of amopyroquanine. But, we should prefer to start in the middle of the molecule to achieve the greatest simplification. Disconnection 1 would require a nucleophilic displacement (X= a leaving group) on an inactivated benzene ring 1. The disconnection requires nucleophilic displacement at position 4 in a pyridine ring, and an acceptable reaction because of the electron-with drawing effect of the nitrogen atom in the ring, so this is the better route, though use may be apprehensive about controlling the chemo selectivity as there are three potential nuclophisles in 4 and two potential electrophiles in 7 and two potential electrophiles in 2.



Scheme 1: Disconnection of amopyroquanine

The synthesis of amopyroquanine can be done by reacting pyrolidine, 4-aminophenol and formaldehyde in Munich reaction process (condensation of an enolite carbonyl compound with imminol ion or condensation of imines with aldhayd or keton) and producing compound 3[21]. The other route of the synthesis is combination of acrylic acid (8) and 3-chlorobenzenamine (7) and producing 7-chloro-2, 3-dihydroquinolin-4(1H)-one (compound 6). Compound 6 can be changed in to compound 2 by FGI (functional group

interconversion). Combination of compound 2 and 3 will give as amopyroquanine 1.



Scheme 2: synthesis of amopyroquanine

Since, the synthesis mechanism of these above structure is starting from the disconnection of the compound amopyroquanine.

4. Mechanism of amopyroquanine action

Although amopyroquanine has been used as an antimalarial agent new a day, the ability of antimalarial drug and other weak bases to raise the PH of acid vesicles has been appreciated only in the last 10 to 20 years. The effect of amopyroquanine on the intra vascular PH of the acid vesicles of the parasite is similar to that of chloroquine. The uptake of amopyroquanine by plasmodium falciparum has not been studied quantitatively, the low nanomolar concentration of amopyroquanine which raises vascular PH in the parasite are inconsistent with its pks and indicate that it cannot be acting only as a weak base. In contrast the micro molar concentrations of amopyroquanine necessary to raise vascular pH in mammalian cells are consistent with its properties as a weak base [22]. Its mechanism of action is to suppress DNA replication and transcription in the parasite, an action like that of many chemotherapist agents.

Plasmodial parasite depends on the breakdown products of the hemoglobin molecule for most of their energy. Thus any drugs which suppress the production of enzymes to do this will be particularly effective [2]. Its activity concentrated by sensitive intra erythrocytic plasmodial: higher concentration is found in infected RBs by accommodating in of the acidic vesicles of the parasite and because of its weakly basic nature. It relies the vascular pH and there by interference with degradation hemoglobin by parasitic lissome [1].

5. Mode of action of amopyroquanine antimalarial

The precise mode action of the quinoline antimalarial is still not completely understood, although various mechanisms have been proposed for the action of amopyroquanine and related compounds. Some of the proposed mechanism would require high drug concentration than those that can be achieved *in vivo* and, therefore, are not consider as convincing as other arguments. Such mechanism includes the inhibition of protein synthesis, the inhibition of food vacuole phosphor lipases, the inhibition of aspartic protein assess and effects on DNA&RNA synthesis.

Amopyroquanine is active against the erythrocytic stage of malaria parasites but not against pre-erythrocytes stage of parasites in the liver or mature gametocytes. Since amopyroquanine acts exhaustively against these stage of the intra-erythrocytic cycle during which the parasite is actually degrading hemoglobin, it was assumed that amopyroquanine somehow interference with the parasite feeding process [23].

6. Metabolic stability and identification of amopyroquanine

The parent compound amopyroquanine is primarily metabolized by N-dealkylation of the ethyl groups on its amino alkyl side chain. This factor promited us to test for significant change in the metabolism of drug candidates, a majority of which carried modifications in this region. For the assessment of metabolic stability each of the compounds was incubated with pooled human liver microsoms in the presence of NADPH, and the disappearance of the parent compound was analyzed.

Amopyroquanine had a longer half-life than any other compounds in their assays. The ring substituted compound with a diethyl amino alkyl side chain analogues. All the side chain with substituted tertiary amine had significantly shorter half-life (<10min). Since amopyroquanine is mostly modified in the side chain modification to the basic side chain may have had a significant effect on the metabolism of these compounds.

Metabolic stability is essential for an effective antimalarial drug and since metabolism path ways can often blocked by chemical modification of the substrate, was used to identify the metabolites of the tertiary amine compounds generated during incubation with human microsoms. The primary metabolites for these analogues resulted from N-dealkylation reaction of both the propyl group and the aromatic group. An important observation was that the metabolites resulting from the N-dealkylation of the propyl group were at least as abundant as those obtained from removal of the beury group [24].

7. Amopyroquanine next-generation candidates in clinical development

4-aminoquinoline based drug development project continue to yield promising drug candidates and several molecules have interested in to pre-clinical development of clinical trials over the last few years. Projects to reduce resistance development of amopyroquanine have resulted in the development of short chin chloroquine analogues, organometalic antimalarial and a "fusion" trioxaquine antimalarial. Projects to reduce the toxicity of amopyroquanine have resulted in the development of metabolically stable amopyroquanine analogue [25].

7. Application of Amopyroquanine

Amopyroquanine have proven to be superior alternative drugs to in areas of high chloroquine resistance (8). Amopyroquanine is an antimalarial compound chemically and functionally related to chloroquine (CQ). Since it has their own applications and some of these are summarized as follows [3].

Amopyroquanine is the drug of choice for clinical cure and suppressive prophylaxis of all types of malaria. Amopyroquanine is manly employed for complicated cerebral malaria in adults. It completely cures sensitive falciparum dieses, but relapses in vivax and ovale malaria are not prevented. In short time visitors to chloroquine sensitive endemic areas, suppressive doses should be started one week before and continued for four weeks after retuning.

- Rheumatoid arthritis
- Extra intestinal amoebiasis
- discoid lubus erythmatous-very effective
- Libra reactions
- Photogenic reactions
- Infectious mononucleosis: affords symptomatic relief

9. Adverse effect of Amopyroquanine

All medicines have side effects. But many people don't feel the side effect, or they are able to deal with them. Side effects are also listed in the information that comes with your medicine [26]. Toxicity of amopyroquanine is low, but side effects are frequent and unpleasant.

- Parental administration can cause hypertsion and cardiac depression.
- Prorogued use of high loses may cause loss of vision due to retinal damage, corneal deposits may also occur and affect vision, but are reversible on discontinuation.
- Loss of hearing, rashes, photoalergy, mental disterbance, myopathy and graying of hair can occur in long term use.
- Sleep disturbance
- Itching
- Blurred vision
- Diarrhea

Amopyroquanine can be used for treatment of malaria during pregnancy and have no abortifacient or teratogenic effect have been reported 3.

10. Conclusion

The rapid spread of drug-resistant malaria worldwide has stimulated the search for new drugs to treat millions of people infected with the parasite. There is an urgent need for antimalarial with novel structures, modes of action, or both, to deal with the development of resistance to the drugs in current use.

This study deals with the synthesis and antimalarial activities of amopyroquanine of antimalarial drugs. The main objective of which is to contribute to efforts being made to search for novel chemotherapeutic drugs that can be used against the resistant strains of P. falciparum.

The newly antimalarial drug amopyroquanine were screened in vitro against four isolates of P. falciparum at various stages of the parasites development. The results showed that amopyroquanine is more active in vitro against the parasites in comparison to chloroquine, the drug of choice for chloroquine faliciparim malaria in Africa.

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