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NEWER TRENDS IN ANTIMALARIAL CHEMOTHERAPY

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ABSTRACT

Di & tri substituted imidazoles were prepared by condensing phenylglyoxal with different aryl aldehydes in presence of ammonium acetate and glacial acetic acid. All the di and tri substituted imidazoles were characterized by spectral analysis i.e. ^{1}HNMR and Mass spectral data. All the synthetic compounds were screened for there anti-inflammatory and anti bacterial activity.

Keywords: Imidazole, Phenyl glyoxal, anti-inflammatory and anti microbial.

1. INTRODUCTION

Malaria is a major parasitic disease affecting around 300-500 million people of which more than one million die every year. **Malaria** is a vector-borne infectious disease caused by ***protozoan parasites***. It is widespread in tropical and subtropical regions, including parts of the Americas, Asia, and Africa. Each year, it causes disease in approximately 515 million people and kills between one and three million people, the majority of whom are young children in Africa. Malaria is commonly associated with poverty, but is also a cause of poverty and a major hindrance to economic development.[1]

Malaria is complex but it is a curable and preventable disease. Lives can be saved if the disease is detected early and adequately treated.

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It is known what action is necessary to prevent the disease and to avoid or contain epidemics and other critical situations. The technology to prevent, monitor, diagnose and treat malaria exists.

Although some are under development, no vaccine is currently available for malaria; preventative drugs must be taken continuously to reduce the risk of infection. Malaria infections are treated through the use of antimalarial drugs, such as quinine or artemisinin derivatives, although drug resistance is increasingly common[2].

2. CAUSES: Malaria is caused by protozoan parasites of the genus *Plasmodium* (phylum Apicomplexa). In humans malaria is caused by *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. *P. falciparum* is the most common cause of infection and is responsible for about 80% of all malaria cases, and is also responsible for about 90% of the deaths from malaria.[3] Parasitic *Plasmodium* species also infect birds, reptiles, monkeys, chimpanzees and rodents.[4]

SYMPTOMS:

Severe malaria is almost exclusively caused by ***P. falciparum*** infection and usually arises 6-14 days after infection. Symptoms of malaria include fever, shivering, arthralgia (joint pain), vomiting, anemia (caused by hemolysis), hemoglobinuria, and convulsions.[5]

3. CURRENTLY USED ANTI-MALARIAL DRUGS:

For the past 50 years, three classes of drugs– quinoline and related quinoline-based antimalarials, antifolates and very recently artemisinin derivatives have formed the mainstay of antimalarial chemotherapy. Following is a brief description of important antimalarial drugs of various classes, their mode of action, uses and limitations.

Currently available anti-malarial drugs include: [6]

- **Artemether-lumefantrine** (Therapy only, commercial names *Coartem*® and *Riamet*®)
- **Artesunate-amodiaquine** (Therapy only)
- **Artesunate-mefloquine** (Therapy only)
- **Artesunate-Sulfadoxine/pyrimethamine** (Therapy only)
- **Atovaquone-proguanil**, trade name **Malarone** (Therapy and prophylaxis)
- **Quinine** (Therapy only)
- **Chloroquine** (Therapy and prophylaxis; usefulness now reduced due to resistance)
- **Cotrifazid** (Therapy and prophylaxis)
- **Doxycycline** (Therapy and prophylaxis)
- **Mefloquine**, trade name Lariam (Therapy and prophylaxis)
- **Primaquine** (Therapy in *P. vivax* and *P. ovale* only; not for prophylaxis)
- **Proguanil** (Prophylaxis only)
- **Sulfadoxine-pyrimethamine** (Therapy; prophylaxis for semi-immune pregnant women in endemic countries as "Intermittent Preventive Treatment" - IPT)
- **Hydroxychloroquine,** trade name Plaquenil (Therapy and prophylaxis)

4. NATURALLY OCCURING ANTIMALARIAL DRUGS:

4.1 QUINOLINE AND RELATED ANTIMALARIALS

Quinine

Quinine 1 (Fig. 1) is an effective antimalarial, isolated from the bark of American Cinchona tree, which was first imported into Europe from Peru for antimalarial use in the seventeenth century. It is a blood schizontocide. Though quinine **1** is highly soluble in water, it can be given intravenously when patients are unable to tolerate oral medication. Though curative to ***falciparum*** malaria, it suppresses but fails to cure or provide prophylaxis against *vivax* malaria. It destroys the trophozoites present in the erythrocytes but has no effect on the exo-erythrocytic stages that develop in the liver. In the case of *vivax* and *ovale* malaria these stages have to be treated with the tissue schizontocide primaquine. The combined treatment with both a blood and tissue schizontocide is called radical cure of malaria.

Chloroquine

Chloroquine 2 (Fig. 1) is a 4-amino quinoline, and is very effective antimalarial. It was first used in the 1940s shortly after the Second World War and was effective in curing all forms of malaria. Chloroquine (CQ) remained the best drug for a long time because of excellent clinical efficacy, few side effects and cost effective synthesis. It is

believed to act by inhibiting heme polymerization. Unfortunately most strains of ***falciparum*** malaria are now resistant to this drug.

Mefloquine

Mefloquine (LARIAM) **3** (Fig. 1) is a product of the Malaria Research Program established in 1963 by the Walter Reed Army Institute for Medical Research. It was first used clinically in 1975. **Mefloquine** is a quinoline methanol derivative and is structurally related to quinine. It is administered orally and has long half life.

Mefloquine appears to act by inhibiting heme polymerase. It is selectively active against the intraerythrocytic mature forms (trophozoites and schizonts) of malaria and has no activity against mature gametocytes. Both in vitro and in vivo resistance has been reported against Mefloquine in malaria endemic regions and the mechanism of resistance may involve the ***P. falciparum*** MDR gene family.

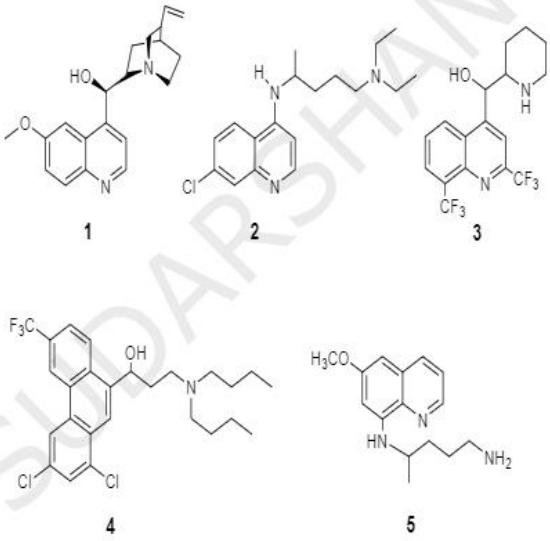


Fig. 1 Quinoline and related antimalarials

Halofantrine

Halofantrine (HALFAN) **4**, (Fig. 1) a phenanthrene methanol analog that is a recent addition of antimalarial to treat (MDR) ***P. falciparum.*** In vitro, it is more active than Mefloquine and was introduced in 1984 when clinical trials began against ***P. falciparum***. It is used for treating mild to moderate acute malaria in sensitive strains of ***P. falciparum*** and ***P. vivax***. Exact mode of action of **Halofantrine** is not yet known. Cure rates were varied and high recrudescent rates were observed. Recent reports have raised serious questions concerning its safety.

Primaquine

Primaquine 5 (Fig. 1) is widely used 8-amino quinoline. It is an effective tissue schizontocide, used for its effect on the liver stages of the parasite's life cycle. The use of this vital 8-amino quinoline is imposing great limitations because of inherent side effects like haemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient cases, anaemia and methaemoglobin toxicity. Besides these *P. vivax* strains showing resistance to this drug from different continents have emerged.

4.2 ANTIFOLATES

Diaminopyrimidines

This class includes compounds like pyrimethamine and trimethoprim.

Pyrimethamine 6 (Fig. 2) is a 2,4-diaminopyrimidine derivative. It is always given in combination with either a sulphonamide or sulfone. It inhibits the activity of dihydrofolate reductase (DHFR). It is active against asexual blood stages of all types of malaria and also active against primary exoerythrocytic stages. The antifolate combination (FANSIDAR) of pyrimethamine 6 and sulphadoxine 10, has been used extensively for prophylaxis and suppression of human malarias especially those with chloroquine (CQ) resistant *P.*

falciparum strain. Resistance and serious **side effects to fansidar is now widespread and therefore it is not recommended.**

Trimethoprim 7 (Fig. 2) is also a 2,4-diaminopyrimidine derivative. It inhibits the activity of dihydrofolate reductase (DHFR). It is effective against asexual blood stages of certain species but is less effective than pyrimethamine. It is always employed as base and in combination with sulfalene **11** (sulpha drug).

4.3 Biguanides

Proguanil 8 (Fig. 2) is the best compound of this series. **Proguanil** (PALUDRINE) is the common name for chloroguanide, a biguanide derivative that emerged in 1945 as a product of British antimalarial drug research. The antimalarial activity of proguanil was ascribed to cycloguanil **8a** (Fig. 2), an active cyclic triazine metabolite shown to be selective inhibitor of the bifunctional plasmodial dihydrofolate reductase – thymidylate synthetase thereby inhibiting DNA synthesis and depleting folate cofactors. Proguanil is effective against the primary exoerythrocytic forms of ***P. falciparum*** and asexual blood forms of all species of human malaria parasite.

4.4 Sulphonamides and Sulfones

These include **sulphadiazine 9**, **sulphadoxine 10, sulphalene 11, dapsone 12** and **acedapsone 13** (Fig. 2). These are basically antibacterials but have shown antimalarial activity during World War II. Malaria parasites, like many bacteria are unable to utilize preformed folic acid and require *p*-amino benzoic acid as a substrate in order to synthesize it. Sulphonamides and sulfones act as competitive antagonists of this substrate. These are slow acting blood schizontocide that are more active against ***P. falciparum*** than ***P.vivax***. These compounds are used in combination with DHFR inhibitors to enhance their antiplasmodial action. Recent reports have shown that *P. falciparum* has developed resistance against antifolates and sulphonamides have found to show serious toxicity in some individuals.

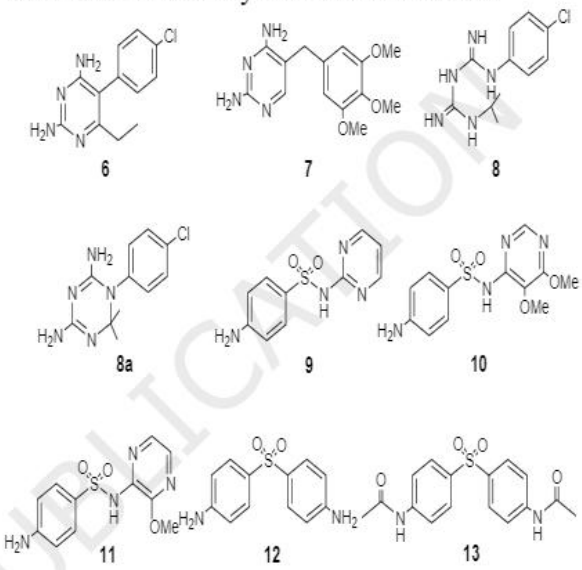


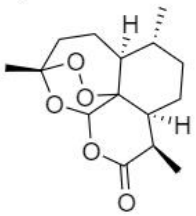
Fig. 2 Antifolates

4.5 Trioxane as antimalarials:

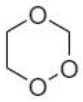
The major breakthrough in the chemotherapy of malaria occurred when in 1971, Chinese scientist isolated Artemisinin from traditional Chinese herb, ***Artemisia annua.***[7]

Artemisinin 14 (Fig. 3) was isolated from the leafy portion of ***Artemisia annua*** in 1971 by Chinese chemists. It is a sesquiterpene lactone endoperoxide. **Artemisinin** is very effective and safe against chloroquine (CQ) sensitive and chloroquine (CQ) resistant strains of ***P. falciparum*** but has certain limitations like poor oil and water solubility and high rate of recrudescence. Hence a lot of efforts have been put to develop semi synthetic derivatives of **artemisinin**.

The peroxide linkage which is responsible for the antimalarial activity.1,2,4-trioxanes is the main pharmacophore of Artemisinin responsible for antimalarial activity.



Artemisinin

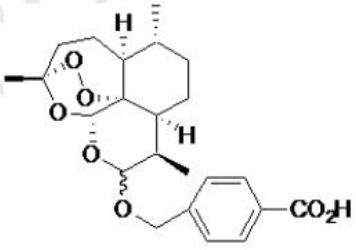


1,2,4-trioxane

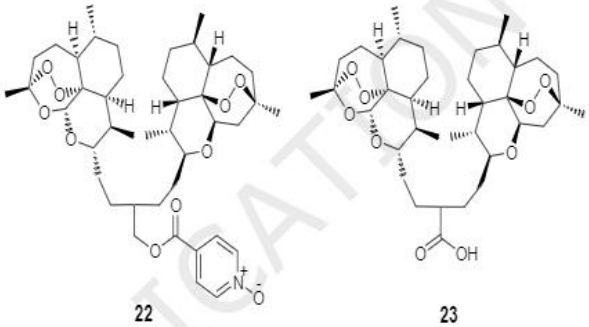
1,2,4-trioxanes are the compound which uses the pharmacophore of the artemisinin, these compounds also suppose to have good antimalarial activity. Several of these trioxanes shows promising antimalarial activity.[8]

Artemisinin was isolated from the leafy portion of ***Artemisia annua*** in 1971 by Chinese chemists. It is a sesquiterpene lactone endoperoxide. **Artemisinin** is very effective and safe against chloroquine (CQ) sensitive and chloroquine (CQ) resistant strains of ***P. falciparum***.

Lin et al. have synthesized several water soluble and hydrolytically stable derivatives of dihydroartemisinin.Among them artelinic acid shows better in vivo activity.[9]

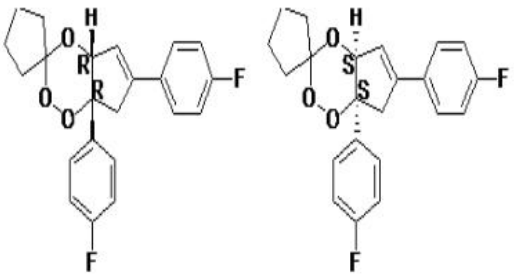


Posner et al. have prepared artemisinin derived trioxane dimers **22** and **23**. In mice both **22** and **23** were more effective than clinically used Artesunate *via* both oral (p.o.) and intravenous (i.v.) administration.[10]

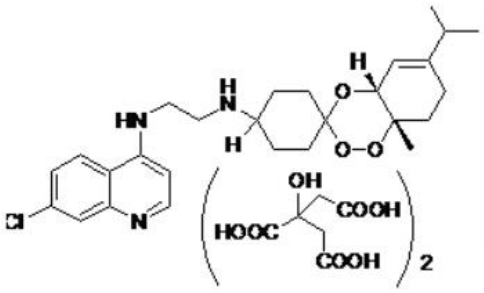


22 **23**

Jefford et al. were the first to report in vitro antimalarial activity of simple 1,2,4-trioxanes. To study the role of chirality on antimalarial activity, the same compound was resolved in to enantiomers using chiral HPLC. As can be seen from the activity profile of each enantiomer, both have almost similar activity.[11]



Meunier et al. have synthesized several trioxane-quinoline 'hybrids' (the so called trioxaquines), some of which have shown promising activity profile in vitro and in vivo.[12]



Singh et al. have prepared several in vivo potent spiro 1,2,4-trioxanes of different prototypes and were the first to report antimalarial potency of synthetic 1,2,4-trioxanes in vivo.[13]

5. FUTURE OUTLOOK OF ANTIMALARIAL DRUGS:

The future outlook for antimalarials by drug discovery could be either through inhibition of MSP 1-pro-cessingprotease, third-generation antifolate malaria drug combinations, ***Plasmodium falciparum*** fatty acid biosynthe-sis,inhibition of malaria lactate dehydrogenase, inhibition of phospholipids metabolism, or ***P. falciparum*** protein farne-syl (transferase inhibitors). However, it may take over5 years to discover a truly new antimalarial drug (Table 1).In contrast, new developments using existing antimalarial drugs might involve a shorter period (3–5 years). This includes the following: development of intravenous artemisinin (artelinate) derivative for severe malaria; development of an artesunate/dihydroartemisinin suppository; development of an artesunate-sulfadoxine/pyrimethamine,artesunate-amodiaquine,artesunate chlorproguanil-dapsone combination; development of a synthetic endoperoxide; development of isoquine (4-aminoquinoline), and development of artesunate-pyronaridine in combination and artesunate/di-hydroartemisinin-piperaquine.[14]

6. CONCLUSION

Although several individual and combination drugs therapies are available against malaria, each has its limitations due to one or more of the associated liabilities e.g. toxicity, resistance, and/or cost.

However, Artemisinin and its derivatives are associated with serious problems of high rate of recrudescence and limited availability from natural sources.With the establishment of the fact that Artemisinin and its derivatives owe their antimalarial activity to the peroxide group present as 1,2,4,-trioxane, there has been an increased interest in the synthesis and biological evolution of organic peroxides particularly1,2,4,-trioxanes.

Although some are under development, no vaccine is currently available for malaria; due to the parasites rapidly increasing resistance to such standard drugs. So preventative drugs must be taken continuously to reduce the risk of infection.

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