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RECENT UPDATE ON USE OF NATURAL PRODUCT AS AN ANTI-MALARIAL AGENT

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ABSTRACT

Malaria remains a formidable global health challenge, particularly in regions where the disease is endemic, and conventional anti-malarial treatments face challenges such as emerging drug resistance. In the quest for more effective and sustainable solutions, natural products have emerged as a compelling area of research for their potential as anti-malarial agents. Malaria is caused by Protozoan Parasites have the genus Plasmodium. The Life Cycle of Malaria is in two phases i.e., in the mosquito vector and the vertebrate hosts. Malaria is transmitted through the bite of an infected womanish Anopheles mosquito. Quinine is the 1st alkaloid which is isolated from Cinchona tree it led to discovery of synthetic chloroquine, mefloquine.

SAR study on the chemistry and antitumor exertion of fused nitrogen heteroaromatic composites, a series of direct, methyl- substituted derivations of 5H- and 6 Hindolo (2,3- blquinolines were synthesized according to the modified Graebe- Ullmann response. To establish the relationship between the physicochemical and natural conditioning of indole- 2,3- blquinolines, their lipophilic parcels, cytotoxic and antimicrobial exertion, and capability to induce topoisomerase I1 dependent pSP65 DNA fractionalization in vitro were delved. We set up that the antimicrobial and cytotoxic exertion of indole (2,3- blquinolines was explosively told by the position, and the number of methyl substituents and the presence of methyl group at pyridine nitrogen was essential for the cytotoxicity of these composites. All indolo- 2,3- blquinolines belonging to the 5H series

CHAPTER 1

1.1 Introduction

Herbs and the plant source are been used as a source of drug throughout history and continue to serve as the base for numerous medicinal used moments. The medicinal parcels of shops are described formerly on Assyrian complexion tablets dated about 2000B.C. and proved in the Egyptian culture, the Indian Ayurveda. (1) Malaria remains a redoubtable global health challenge, particularly in regions where the complaint is aboriginal, and conventional anti-malarial treatments face challenges similar as arising medicine resistance. In the hunt for further effective and sustainable results, natural products have surfaced as a compelling area of exploration for their eventuality as anti-malarial agents. (5)

Malaria remains one of the most significant health issues that we face moment, with 250 million cases, and over 800,000 deaths annually. The current gold standard drug is the fixed cure artemisinin combination remedy conforming of chemical derivations of the Chinese natural product artemisinin, and a longer acting mate (an arylamino alcohol or 4- amino quinoline), which eventually traces its strain back to the natural product quinine, Cinchona nor Artemisia excerpts on their own would meet these criteria. sanctification, chemical revision, expression and combination of these natural products produces bettered drugs with> 95 cure rates after three days of treatment, but this has taken numerous times of development work. (2)

Malaria transmitted by womanish Anopheles mosquitoes has four Plasmodium species as its aetiological agents –P. falciparum, P. vivax, P. ovale and P. malariae, the most wide and severe complaint is caused by P. falciparum, which transiently infects the liver before overrunning red blood cells of the mammalian host. (3) The Life Cycle of Malaria is in two phases i.e., in the mosquito vector and the invertebrate hosts. (4) Malaria is transmitted through the bite of an infected womanish Anopheles mosquito. (2)

Life cycle of Malaria

1. A Vector which is a womanish anopheles fit Sporozoites. (4)

2. The Sporozoites attack on the Liver Cell and it get infected. (4)

3. Mature into Schizonts. (4)

4. Ruptured the schizont and release merozoites. (4)

5. After this original replication in the liver, the spongers suffer asexual addition in the erythrocytes, due to which the merozoites infect RBC (Red Blood Cells. (4)

6. The ring stage trophozoites develop into schizonts, which rupture releasing merozoites. (4)

7. Blood Stage spongers are responsible for the clinical instantiations of the complaint. (4)

8. The gametocytes, manly i.e., microgametocytes and womanish i.e., macrogametocytes, are ingested by an ANOPHELES mosquito. (4)

9. Schizonts that develop into trophozoites, convert to gametocytes (4).

10. The sponger's addition in the by sporogonic cycle. (4)

11. Now an active Vector tore-infect. (4)

1.2 History of Natural Product

Anti-malarial chemotherapy history linked with the background of herbal medical products. (2) QUININE the original natural product used in anti-malarial was linked from cinchona tree dinghy, and purified in 1820. (2) Synthesize Quinine as a lead develop of methylene blue. By this farther 4- aminoquinolines and amino- alcohols as Chloroquine, Amodiaquine and Mefloquine which are used as a malarial treatment. (2) Another natural product NAPHTHOQUINONE lapichol was linked as API i.e., Active Pharmaceutical component in tree dinghy to treat malaria, it also helps to discovered of atovaquone. (2)

1.3 Natural Product and their source

Natural Product	Source	Mechanism of Action
QUININE	Cinchona Genus	Same as Chloroquine an prevent heme polymerisation
ATOVAQUONE	Bignoniaceae	Electron Transport inhibition
ARTEMISININ	Artemisia annua	Free ferrous iron liberated in erythrocytes by parasite digestion of haemoglobin

Table 1: Natural Product and their Source with Maximum activity (2)

First Line of medicine use to treat include quinolines, 8- aminoquinolines, antifolates, and endoperoxides. (6) Atovaquone belongs to a naphthoquinone class combination remedy with proguanil i.e., Malarone to treat malaria. As we bandy the chemical nature if quinone is oxidized and hydroquinone is reduced by which it forms fluently inter-convertible and nearly balanced stoutly. (6)

1.4 Natural Quinones and their analogs as Antimalarial Agents

Agents Quinine is the 1st alkaloid which is insulated from Cinchona tree it led to discovery of synthetic chloroquine, mefloquine. Natural Product Quinine (Ex – Cinchona spp), Lapachol (Ex- Tabeuia spp), Artemisinin (Ex- Artemisia annua) (6) Synthetic medicines Chloroquine, Mefloquine, Atovaquone (6) Semi-synthetic medicines Artesunate, Artemether, Arteether (6)

1.5 CHEMICAL STRUCTURE OF ANTI MALARIAL AGENTS

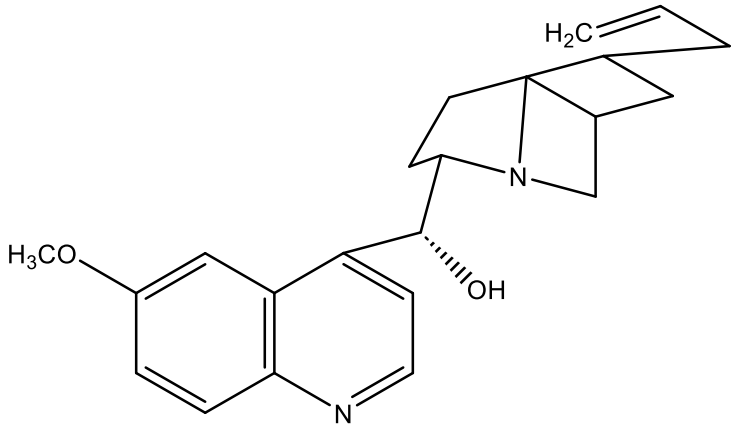


Figure 1: Chemical Structure of Quinine (Cinchona spp) - Natural Product (6)

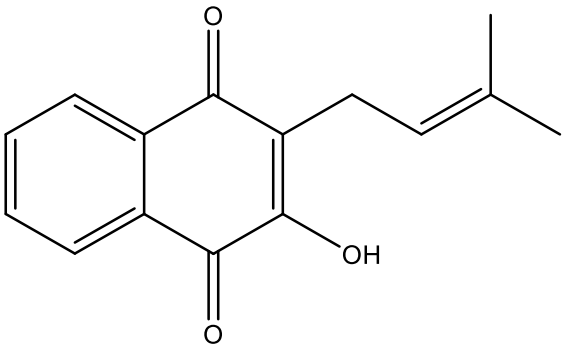


Figure 2: Chemical Structure of Lapachol (Tabeuia spp) Natural Product (6)

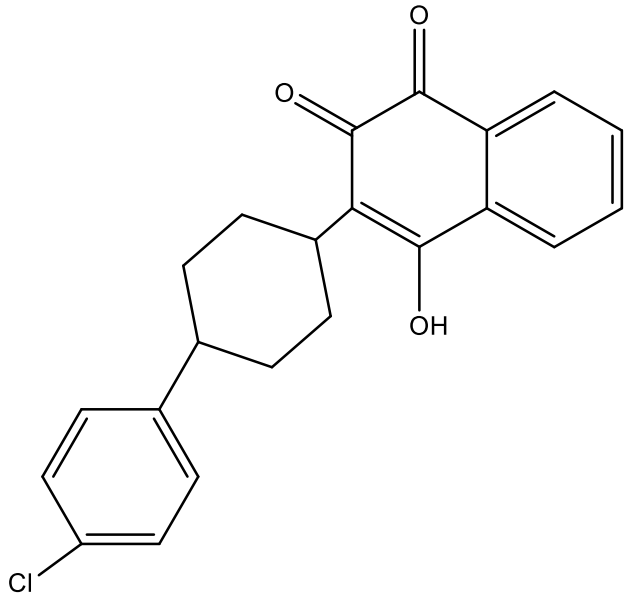


Figure 3: Chemical Structure of Atovaquone – Synthetic Drug (6)

Artemisinin is natural endoperoxide which is insulated from sweet warm wood factory Artemisia annua and its semi synthetic analogues artemether, artether and artesunate are potent antimalarial agent. (7)

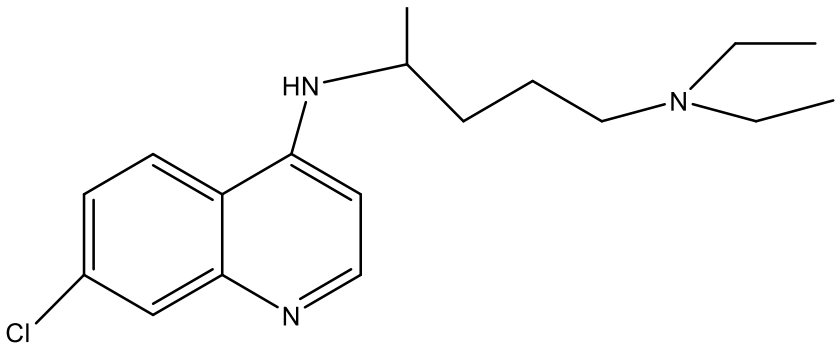


Figure 4: Chemical Structure of Chloroquine (7)

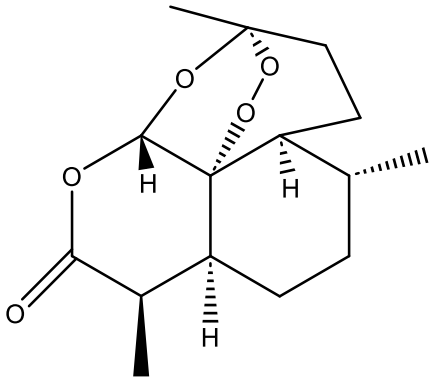


Figure 5: Chemical Structure of Artemisinin (8)

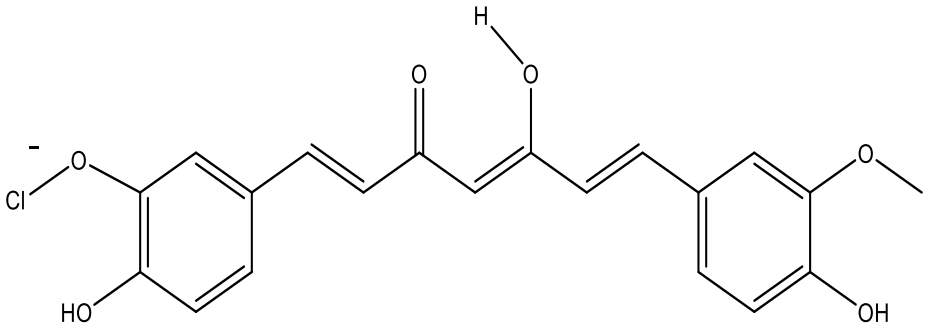


Figure 6: Chemical Structure of Curcumin (8)

1.6 Semi-Synthetic Derivatives

1. Artemisinin: $C_{15}H_{22}O_5$ (10)

Artemisinin's are deduced from excerpts of sweet wormwood (Artemisia annua), treatment of malaria. (9)

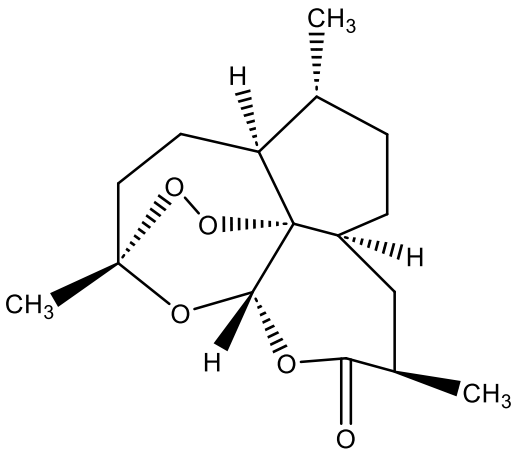
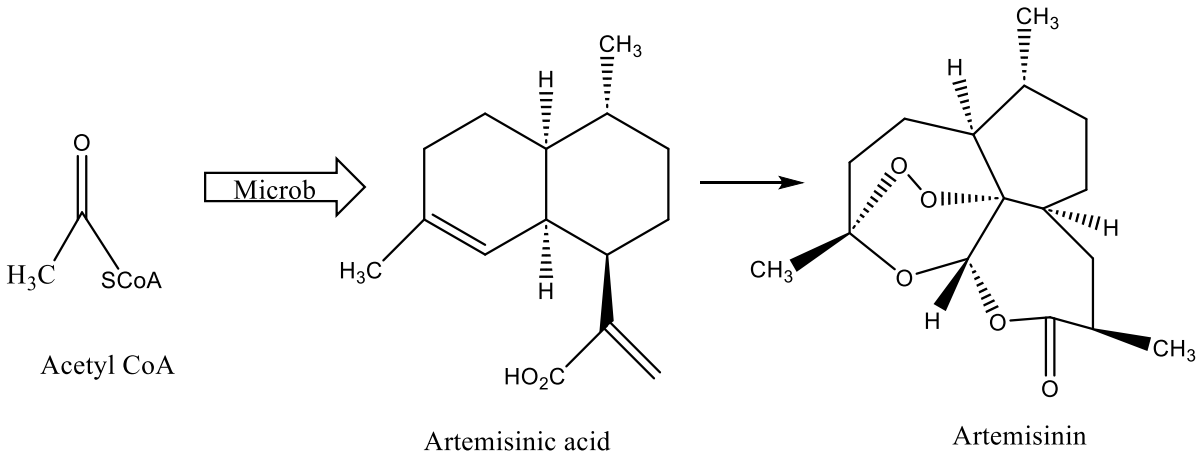


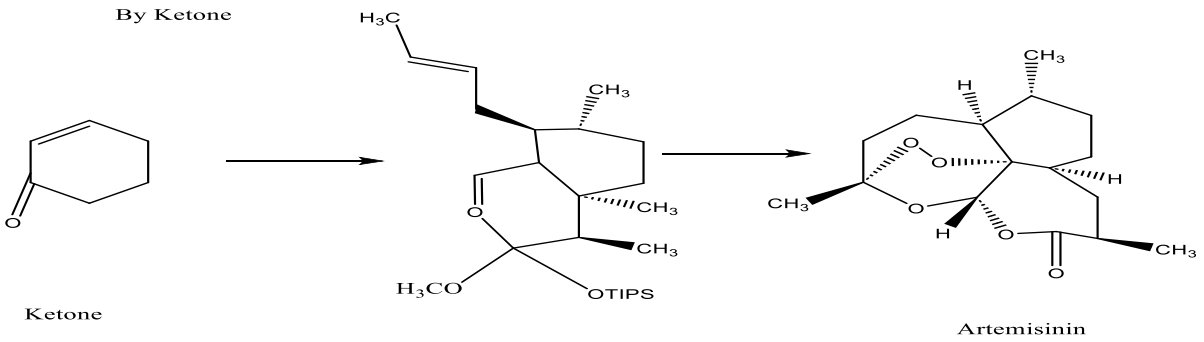
Figure 7: Chemical Structure of Artemisinin (9)

SYNTHESIS OF ARTEMISININ

I. Synthesis by Acetyl CoA (11)

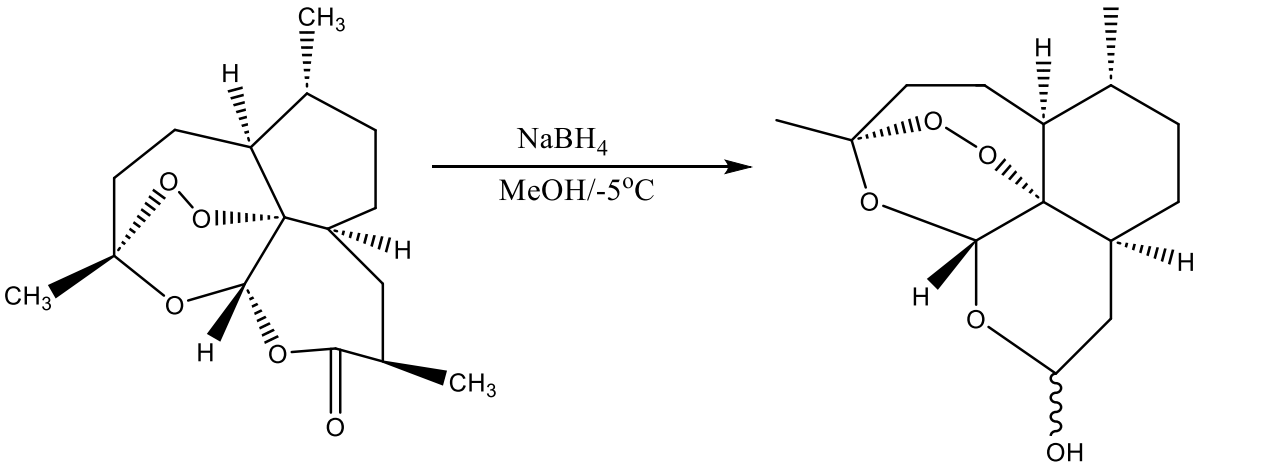


II. Synthesis by Ketone (11)



2. DIHYDROARTEMISININ (12)

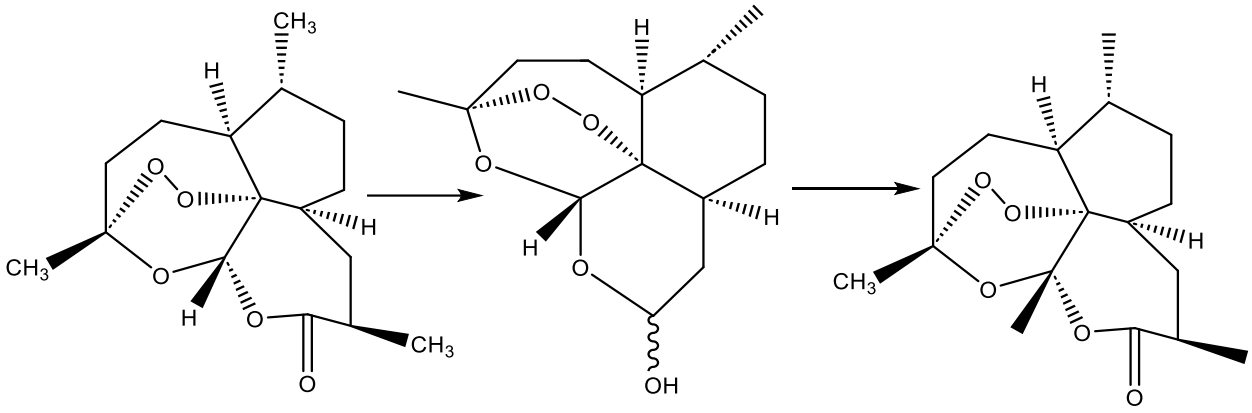
SYNTHESIS



Artemisinin Dihydroartemisinin

3. ARTEMETHER (13)

SYNTHESIS



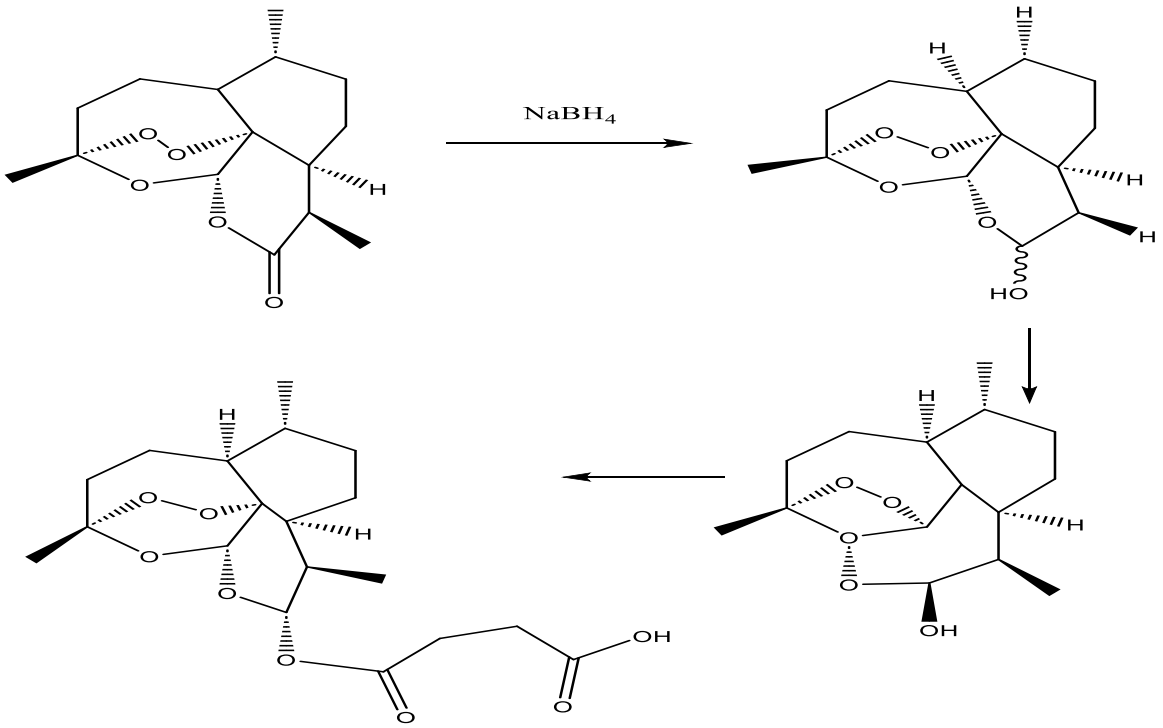
Artemisinin

Dihydroartemisinin

Artemether

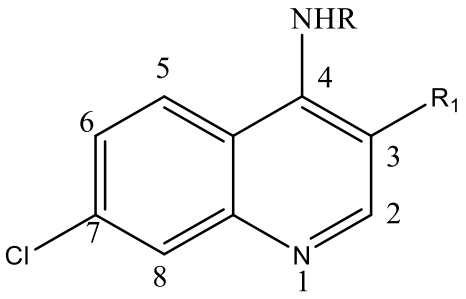
4. ARTESUNATE (14)

SYNTHESIS



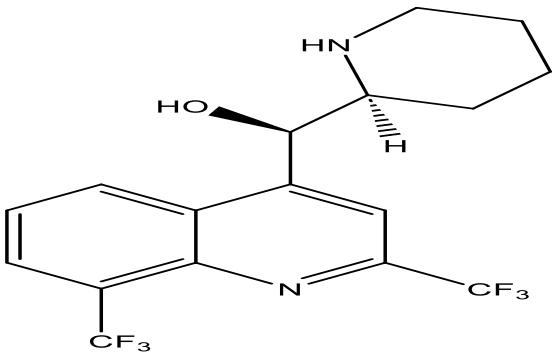
1.7STRUCTURE ACTIVITY RELATIONSHIP (SAR)

1) 4-aminoquinolines (15)



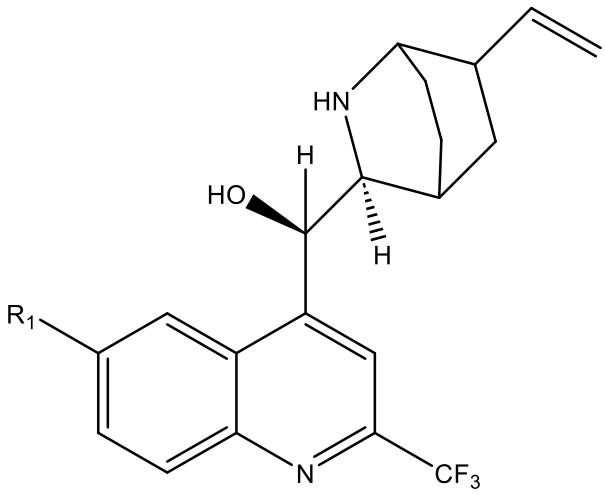
- 2-5 carbon atom between the nitrogen atoms, 4-diethylamino-1-methylbutylamino side chain is optimal for activity as in chloroquine.
- Tertiary amine is important for the activity.
- At 3- position introduction of methyl group reduces the activity.
- Aromatic ring in the side chain reduces the toxicity.
- D-isomer of chloroquine is less toxic than L-isomer

2) QUINOLINE (16)



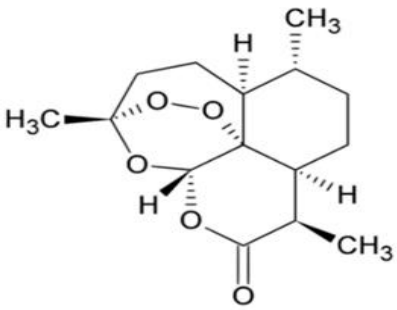
- Mefloquine effective in the treatment and prophylaxis of malaria due to destruction of asexual blood form of malarial pathogens that affect humans

3) QUININE (17)



- Quinoline ring replacement of methoxy group by a halogen, especially chlorine enhances activity.
- At 8-position halogen enhanced the activity.
- Modification of secondary alcohol at C-9, through oxidation esterification diminishes activity.

4) ARTEMISININ (18)



- Tetracyclic Structure with a trioxane ring and a lactone ring.
- Trioxane ring contain peroxide bridge, the active moiety of the molecule for the antimalarial activity.
- Alcohol was derivatized as a mixture of two diastereomers to be separated and by bio assay, biological activity

CHAPTER 2

Literature Review

1. **Hagai Ginsburg et al.** Studied about the natural composites, substantially from shops, have been the dependence of traditional drug for thousands of times, and the explanation for using natural composites for medicine development has been presented with specific consideration of anti-malarial medicines. principles for using medicine combination and the benefits of using multi-component factory excerpts have been arguing. The

scientific and pharmacological defence of these principles could give the base for farther development of ethnical/ traditional drug as a valid, cheap and locally-available means to treat malaria. (1)

2. **Monica Noronha et al.** Studied about the multistage malarial parasite has co-evolved in mosquitoes and the human host. Sponger to develop vaccine to treat malaria, stopgap for chancing a supereminent emulsion is shops. There are numerous factory species which have been left unexplored with its capability to treat malaria ideal malaria vaccine would work by cranking the vulnerable system to kill all the spongers. But this type of protection would be a delicate task to achieve, vaccine inventors have concentrated their work on creating such a vaccine that would limit the sponger to infect other healthy erythrocytes. Cinchona tree contains a element called quinine, which was used to treat malaria. (19)
3. **Kirandeep Kaur et al.** Studied about the recent advances in antimalarial drug discovery from natural sources, including plant extracts, and compounds isolated from plants, bacteria, fungi and marine organisms. Literature compilation from plant and marine extracts, alkaloids (naphthylisoquinolines, bisbenzylisoquinolines, protoberberines and aporphines, indoles, manzamines, and miscellaneous alkaloids) terpenes (sesquiterpenes, triterpenes, diterpenes, and miscellaneous terpenes) quassinoids, flavonoids, limonoids, chalcones, peptides, xanthones, quinones and coumarines, and miscellaneous antimalarials from nature, semisynthetic approaches to antimalarial drugs discovered from natural sources. (20)
4. **V. Vijayakumar et al.** Studied about the heterocyclic composites are extensively current in beast area as well as in factory area and they play colorful places in metabolic processes. A large number of heterocyclic composites are in clinical practice as a medicine, while numerous of them find artificial mileage and hence the mixtures of heterocyclic composites and understanding of the natural significance of specific heterocyclic class will be an intriguing field of synthetic organic druggist. quinoline derivations and about their medicinal operations. Still structural variations to get better parcels are being continued, we've explored the conflation of some quinoline derivations and their unequivocal structural determination through single demitasse-ray diffraction system (21)
5. **Przemysław J et al.** Studied about the Cinchona alkaloids quinine, quinidine, cinchonine, and cinchonidine are available chiral natural emulsion, natural products, these alkaloids are available in multiple diastereomeric forms which are separated on an artificial scale. The preface discusses in short conformational equilibria, traditional separation scheme, biosynthesis, and de novo chemicalsyntheses.t Cinchona alkaloids will continue as one of the pulpits of choice for asymmetric catalytic metamorphoses and chiral recognition. styles for scalable conflation of certain pivotal interceders like 9- epi-aminoalkaloids are likely to render them indeed more useful to increased.

CHAPTER 3

Conclusion

Malaria remains a global health challenge, with millions of people affected by this mosquito- borne complaint each time. The emergence of medicine- resistant strains of the Plasmodium sponger, which causes malaria, has made the hunt for effective treatments indeed more critical. One promising avenue of exploration in the fight against malaria is the use of natural products as anti-malarial agents. Natural products, similar as factory excerpts and composites deduced from microorganisms, have been used for centuries in traditional drug to treat colorful affections, including malaria. These composites frequently retain unique chemical structures and natural conditioning that make them seductive campaigners for medicine development. In recent times, there has been a growing interest in employing the eventuality of natural products to combat malaria, and this has led to significant advances in the field. Artemisinin, a natural emulsion uprooted from the sweet wormwood factory (Artemisia annua), has been a foundation in malaria treatment. Recent exploration has concentrated on developing new derivations and combination curatives to combat artemisinin resistance, which has surfaced in some regions. Quinine, deduced from the dinghy of the cinchona tree, was the first effective treatment for malaria. Experimenters continue to study its parcels and probe the eventuality of new cinchona alkaloids for malaria treatment. The use of natural products as anti-malarial agents continues to be a subject of active exploration and development. These

natural composites offer a different array of chemical structures and mechanisms of action, making them precious coffers in the fight against medicine- resistant malaria strains. While progress has been made in understanding their eventuality, challenges similar as standardization, safety, and scalability of product remain. In the ongoing battle against malaria, it's pivotal to harness the full eventuality of natural products through rigorous scientific disquisition and collaborations between traditional knowledge systems and ultramodern drug. As exploration progresses, the stopgap is that new anti-malarial agents deduced from natural sources will contribute to further effective and sustainable malaria control and treatment strategies.

CHAPTER 4

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