Pharmacological Potential of Quinoline Derivatives as Anti-Malarial Agents

Mr.Vikrant Dalwal[1*], Ms.Palvi Sharma[2], Ms. Shilpa Thakur[3], Ms. Anu Sharma[4], Mr. Lokender Singh[4] , Ms.Deepika kumari[5]

1. Department of pharmaceutical chemistry, School of Pharmacy, Abhilashi University, Chailchowk, Mandi H.P, 175034, India
2. Department of pharmaceutical chemistry, Abhilashi college of pharmacy, Nerchowk, Mandi H.P,175008, India
3. Department of pharmacology, Shiva College of Pharmacy, Chandpur, H.P., 174004, India
4. Department of pharmaceutics, Shantiniketan college of pharmacy, Nerchowk, Mandi, 175008, H.P.

4 Department of pharmaceutics Shatiniketan college of pharmacy, Nerchowk, Mandi, 175008, H.P.

5 Department of pharmacology, Amar Shaheed Baba Ajit Singh Jujhar Singh memorial college of pharmacy, Bela Ropar, Punjab,140111, India

1. vikrantdalwal692@gmail.com, 2. palvisharma78079@gmail.com, 3. st181998@gmail.com 4. anusarma@gmail.com 4. Lokendersingh850@gmai.com, 6. deepikathakur86289@gmail.com

ABSTRACT:

Due to its many uses in industrial and synthetic organic chemistry, quinoline has recently emerged as a significant heterocyclic molecule. Quinoline is a vital component for the growth of novel drugs and has a greater impact on medicinal chemistry. This unit is used in the synthesis of many marketed drugs. Quinoline, also known as benzopyridine, is a weak tertiary base. Quinoline rings have a variety of properties, including antimicrobial, antimalarial, antifungal, anticonvulsant, and anti-inflammatory properties. There are well-established reactions for the synthesis of quinoline. This review focuses on the antimalarial properties of quinoline derivatives.

KEYWORDS: *Anti-malarial, Heterocyclic compound, Quinoline, Medicinal chemistry, Drug discovery.*

INTRODUCTION:

Runge found quinoline as one of the several components derived from coal tar in 1834[1]. Quinoline, also known as benzopyridine. It is a heterocyclic aromatic molecule containing nitrogen heteroatoms that acts as a weak tertiary base, forms salts with acids, and undergoes electrophilic substitution processes such as pyridine and benzene. Pure quinoline, also known as benzo pyridine, is colourless, with a pKa of 4.85 in water at 20°C. When exposed to light, it darkens. pKa is 4.85, which indicates that it is acidic[2]. It is one of the N-containing motifs that has received the most attention to date and is most frequently found in a variety of natural products, the most popular of which are the alkaloids and pharmacologically active compounds from the Cinchona plant, which exhibit a broad range of biological activity[3]. Quinoline scaffold is an alkaloid substance found in a variety of, medicines, dyes, and other natural goods[4]. The presence of nitrogen atoms considerably improves the fundamental characteristics of compounds containing quinolines[5]. With the chemical formula C9H7N, it features a distinctive double-ring structure with a benzene ring joined to a pyridine moiety[6]. The quinoline ring has been shown to possess antimalarial, antibacterial, antimicrobial, antispasmodic, cardioprotective, anticonvulsant, and analgesic activity[7].

Many chemists from all over the world discussed the importance of quinoline and its derivatives utilizing the synthetic techniques and biological activities of the quinoline skeleton Structure of quinoline is shown in fig no.1.

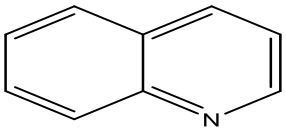


Fig no.1: Quinoline

Methods of synthesis:

There have been numerous preparations for synthesizing quinoline as well as its analogues discovered since the late 1800s. Quinoline's structural core has been synthesised in a variety of ways, including various reactions. [8]

Skraup/ Doebner synthesis:

An aniline and glycerine-based quinoline synthesis employing a strong acid and an oxidant under reflux was described by Skraup and colleagues. A crotonaldehyde intermediate is produced in situ from glycerol in this experiment. Aniline is then added to the process while it is being heated to produce quinoline. In the Doebner-von Miller reaction, aniline and substituted acrolein react to form quinoline in the presence of an oxidant(fig no.2).

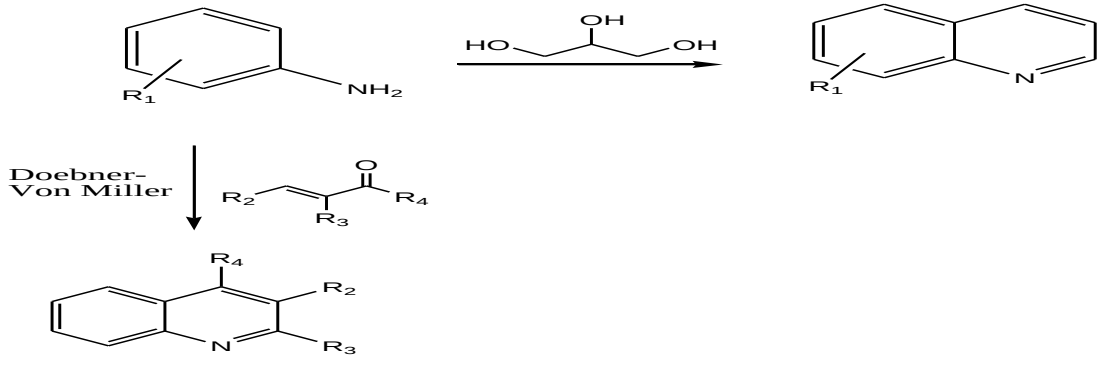


Fig no.2: Skraup/ Doebner synthesis

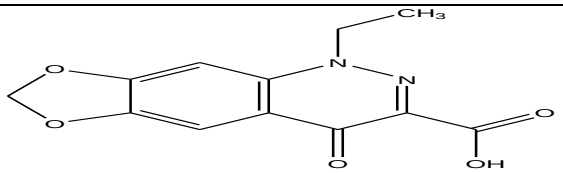
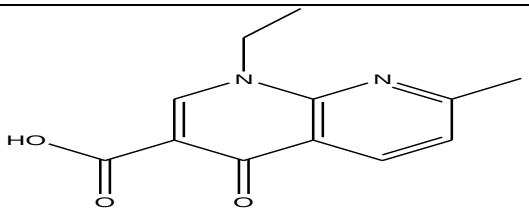
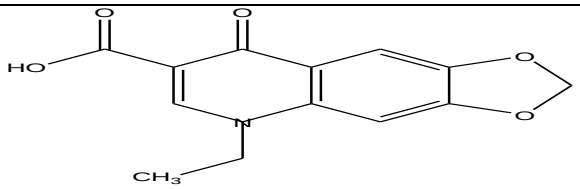
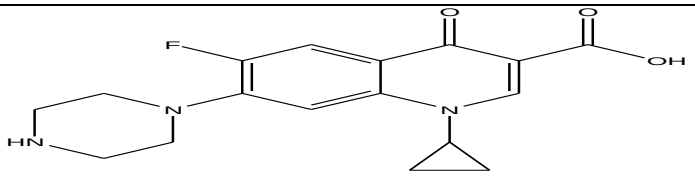
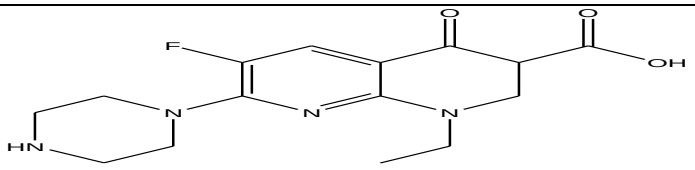
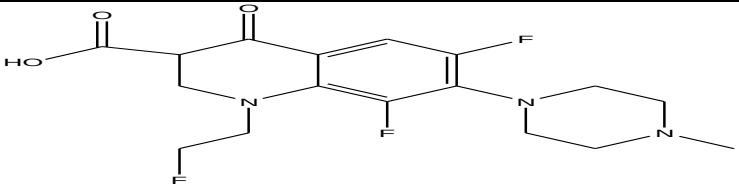
Natural sources of quinoline:

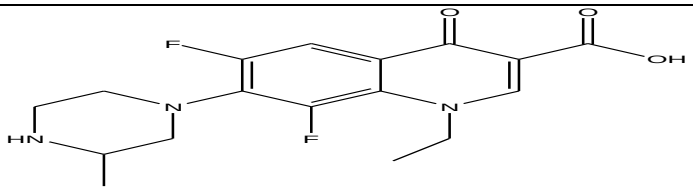
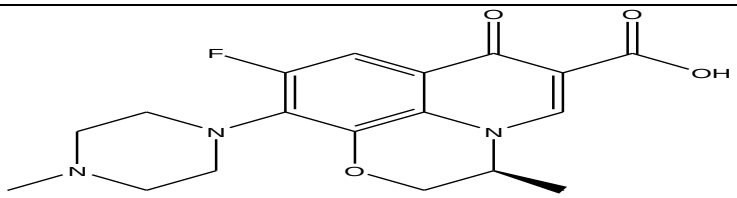
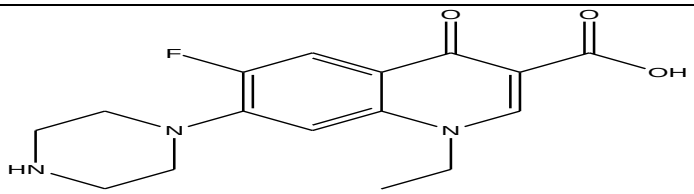
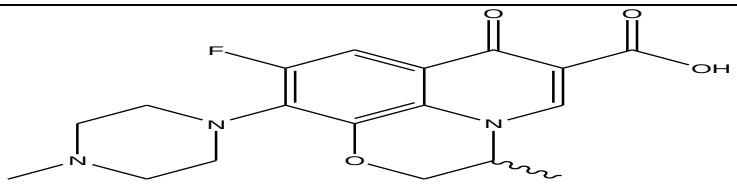
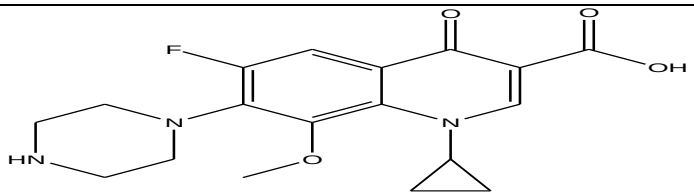
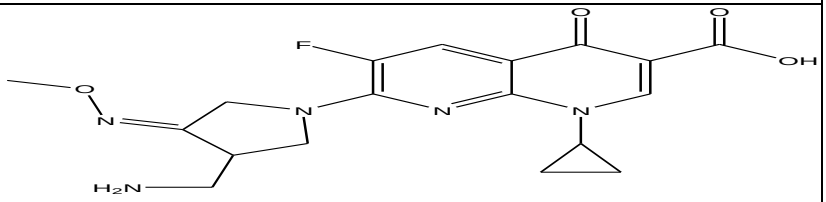
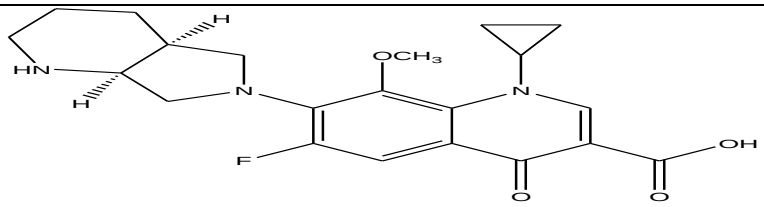
Chinoline alkaloids, which are present in Cinchona bark, are still used in medicine as antimalarial and antiarrhythmic medications.[9] Wall discovered camptothecin, a quinoline alkaloid, in 1966 while conducting a systematic search for anticancer medicines in natural materials. [10]

Quinoline-based approved drugs:

Many medications used in development for the treatment of various disorders contain the quinoline-containing system as a structural characteristic. Quinoline is also found in several therapeutically utilised medications, with antimalarial treatments being the most common. Since the 1940s, antimalarial medications have relied on the aminoquinoline scaffold. Chloroquine was the first medication in this class[11](table no.1).

Table no.1: Quinoline-based approved drug

Quinoline Drug	Activity	Structure
Cinoxacin	Antibacterial activity[12-13], Antimicrobial activity[14]	
Nalidixic acid	Antitubercular activity[15], Antibacterial activity[16], Antibiotic activity[17]	
Oxolinic acid	Antimicrobial activity[18], Antibacterial activity.[1920]	
Ciprofloxacin	Antibacterial activity[21], Antimicrobial activity[22]	
Enoxacin	Antibacterial activity[23]	
Fleroxacin	Antibacterial activity[24], Antimicrobial activity[25]	

Lomefloxacin	Antibacterial activity[2627], Antimicrobial agent[2829]	
Levofloxacin	Antibacterial activity[30]	
Norfloxacin	Antibacterial activity[3132], Antituberculous activity[33]	
Ofloxacin	Antibacterial activity[34], Antimycoplasmal activity[35], Antituberculosis activity[36]	
Gatifloxacin	Antibacterial activity[37]	
Gemifloxacin	Antibacterial activity[38]	
Moxifloxacin	Antimycobacterial activity[39]	

Antimalarial activity:

Chibale et al. developed amine and urea analogues of ferrochloroquine with variable methylene spacer lengths, which were tested in vitro against the Plasmodium falciparum strain(fig no.3). The bulk of analogues proved to be more strong than chloroquine in both strains. Efficacy against malaria was significantly affected by the length of the methylene spacer[40].

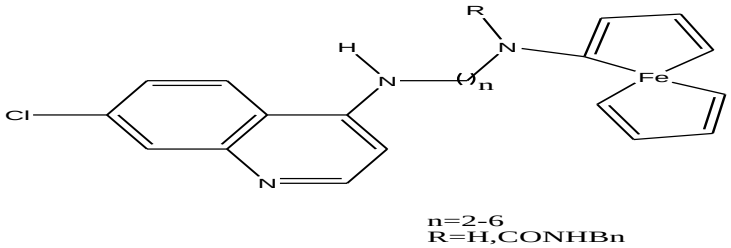


Fig no.3: Amine and urea analogues of ferrochloroquine.

Two quinoline analogues were examined by B. Sureshkumar et al. for spectroscopic characterization and reactivity using DFT and molecular dynamics simulations as potential lead compounds for antimalarial drugs [41](fig no.4).

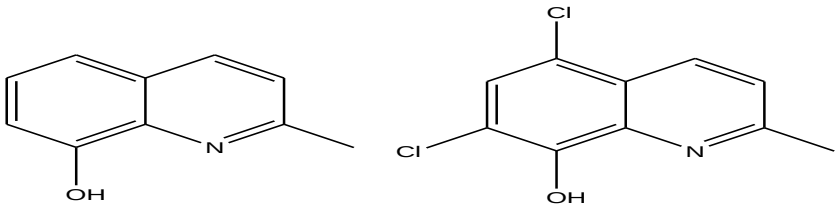


Fig no.4: quinoline analogues.

Mahajan A et al. have synthesised numerous 7-chloroquinolinyl thioureas with excellent antimalarial activity[42](fig no.5).

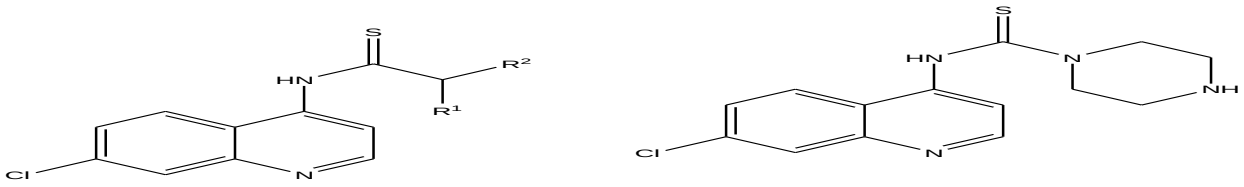


Fig no. 5: synthesise of 7-chloroquinolinyl thioureas derivative.

H.Shiraki et al. developed and tested a series of 5-aryl-8-aminoquinoline (171) compounds for antimalarial activity(fig no.6).[43]

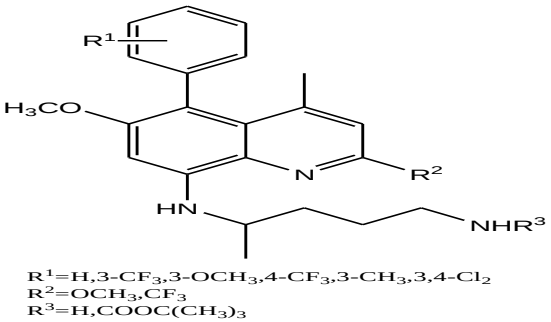


Fig no.6: Synthesis of 5-aryl-8-aminoquinoline derivative.

Singh B et al. developed anti-malarial 4-anilino-quinolines(fig no.7) that illustrated good anti-malarial activity against chloroquine-sensitive P. falciparum strains[44].

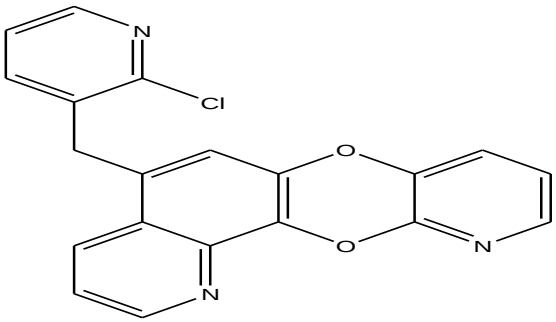


Fig no.7: Synthesis of 4-anilino-quinolines derivatives

A substance called MMV665909 from Medicines for Malaria Venture was reported by Vallieres C et al. The body of information points to MMV665909 as a promising therapeutic candidate and suggests that translation fidelity is an innovative target of antimalarial action [45].

A new antimalarial chemotype is described by Kelly JX et al. Studies conducted both in vitro and in vivo demonstrate that the substance (3-chloro-6-(2-diethylamino-ethoxy)-10-(2-diethylamino-ethyl)-acridone) has effective antimalarial activity against parasites that are sensitive to quinoline as well as those that are resistant to it. [46].

Tim Van et al. synthesize five new aminoquinoline derivatives(fig no.8). In vitro studies show good anti-Plasmodium activities against P. falciparum strains K1 and NF54, both of which are chloroquine-resistant. For this reason, these five new aminoquinoline hit structures are extremely valuable for antimalarial research and have the potential to be developed into new antimalarial drugs with future research[47].

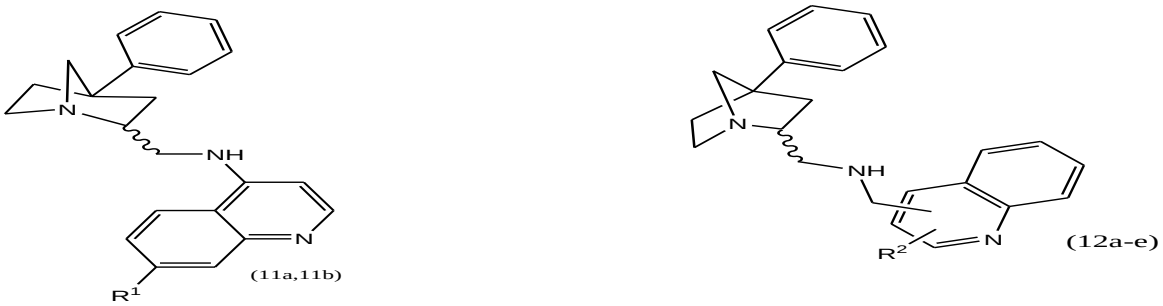


Fig no.8: Synthesize five new aminoquinoline derivatives

Palla D et al. synthesized a collection of FSM analogues (fig no.9) and evaluated them against the chloroquine-resistant strain P. falciparum Colombia. After a biological evaluation, four new compounds with greater antimalarial activity than FSM were found [48].

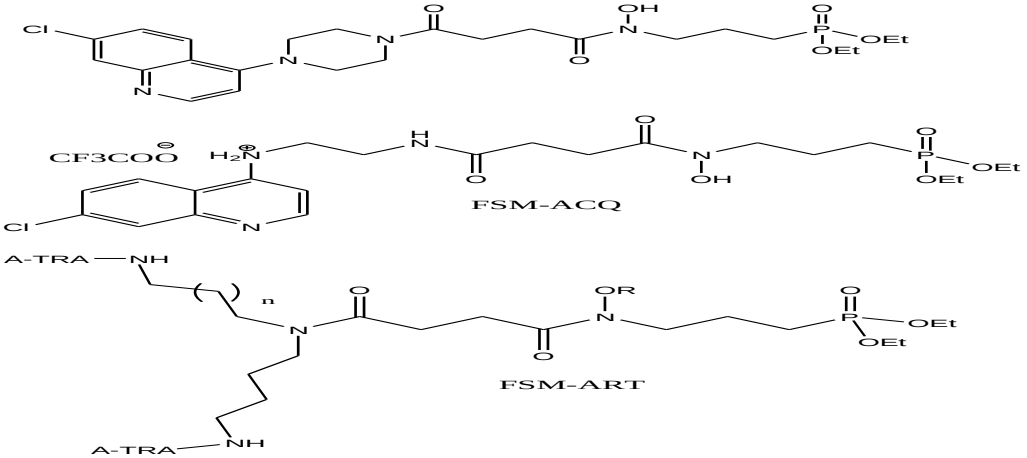


Fig no.9: Synthesized a collection of FSM analogues

Pinheiro L. et al. created new hybrids between chloroquine and sulfadoxine(fig no.10), which resulted in a significant prototype that exhibits greater antimalarial activity than both chloroquine and sulfadoxine[49].

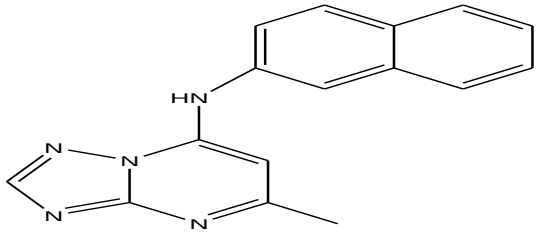


Fig no.10: New hybrids between chloroquine and sulfadoxine

A novel series of dihydropyridines (DHPMs) derivatives (fig no.11) containing quinolinyl residues was reported by Radini IAM et al. synthesized. The compounds showed outstanding antimalarial activity against Plasmodium falciparum. [50]

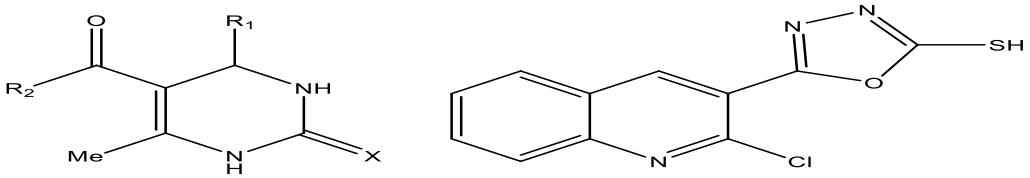


Fig no.11: Dihydropyridines (DHPMs) derivatives containing quinolinyl

Nopol-based quinoline derivatives (fig no.12) were reported by Nyamwihura RJ et al. for their inhibitory activity against Plasmodium falciparum. The nopyl-quinolin-8-yl amides were active against the asexual blood phase of the chloroquine-sensitive strain Pf3D7[51].

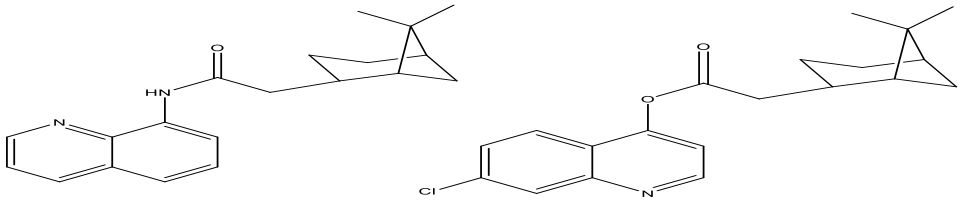


Fig no.12:Nopol-based quinoline derivatives

A series of pyridyl-vinyl quinoline-triazole analogues (fig no.13) have been synthesized by Huang G et al. At low submicromolar concentrations, most chemicals have marked inhibitory effects on the drug-resistant Dd2 strain of malaria. Compound A is the strongest analogue with an EC50 value of 0.04 0.01 M[52].

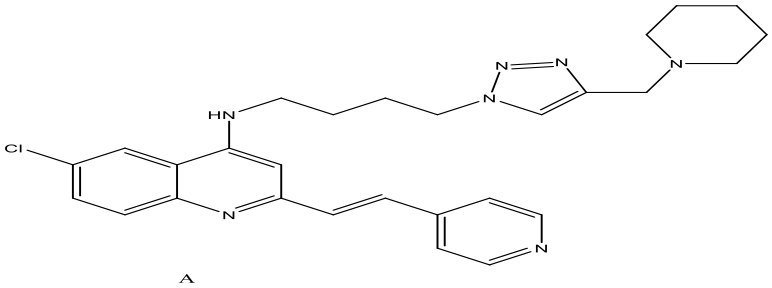


Fig no.13:Pyridyl-vinyl quinoline-triazole analogues

A new category of endoquine-related antimalarials, the 4(1H)-quinolone ester derivatives (fig no.14), are described by Zhang Y et al. With a focus on improving both antimalarial efficacy and bioavailability [53].

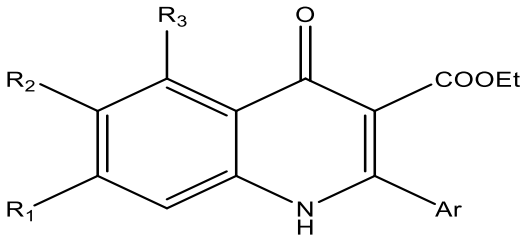


Fig no.14: 4(1H)-quinolone ester derivatives

Nilsen et al. Discovered an effective category of orally active antimalarial 4(1H)-quinolone-3-diaryl ethers (fig no.15). This finding led to the rational design of highly selective ELQs with outstanding oral efficacy against murine malaria[54].

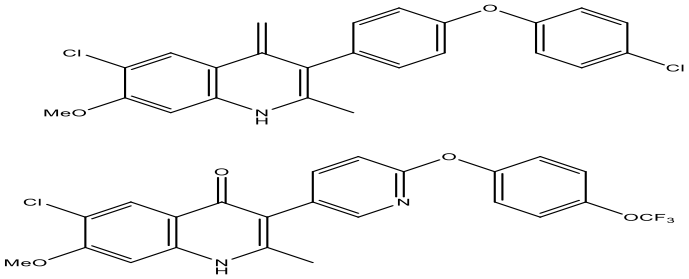


Fig no 15: 4(1H)-quinolone-3-diaryl ethers

Kondaparla S et al. describe a group of novel quinoline-4-amine linked 7-chloro-4-aminoquinoline compounds (fig no.16) spanning various amino acids. The results imply that bis-quinolines may be explored for further research and development as novel antimalarial drugs effective against P. falciparum which is chloroquine-resistant[55].

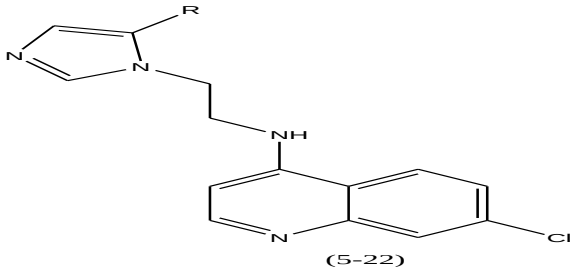


Fig no16: quinoline-4-amine linked 7-chloro-4-aminoquinoline compounds

Mulli C. et al. synthesized and evaluated a collection of enantiopure 4-amino alcohol quinoline derivatives (fig no.17). The S-enantiomers were observed to be active as both chloroquine and MQ.[56]

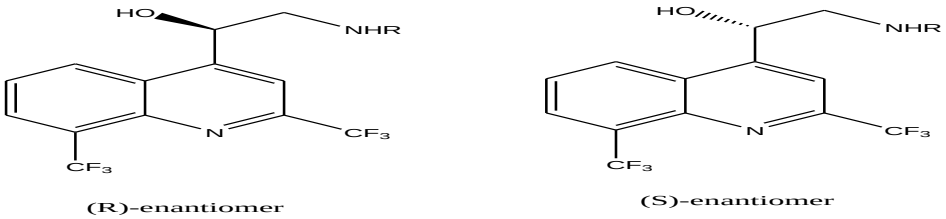


Fig no.17: 4-amino alcohol quinoline derivatives

A sequence of quinoline-4-carboxamides is reported by Baragaa B et al. described. In the P. berghei malaria mouse model, numerous drugs with improved pharmacokinetic profiles have shown excellent oral efficacy with ED90 values below 1 mg/kg[57].

Monastyrskyi A et al. synthesized 4(1H)-quinolone,1,2,3,4-tetrahydroacridone, andphenoxyethoxy-4(1*H*)-quinolone chemotypes(fig no. 18). The synthesized compounds have good antimalarial activity[58].

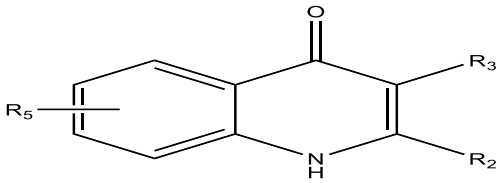


Fig no.18: 4(1H)-quinolone,1,2,3,4-tetrahydroacridone

Guillon J et al. developed and synthesised (fig no.19) some novel quinoline compounds. The most effective antimalarial compound was found to be 2,4-bis[(2-dimethylamino ethyl)amino-methyl]phenylquinoline[59].

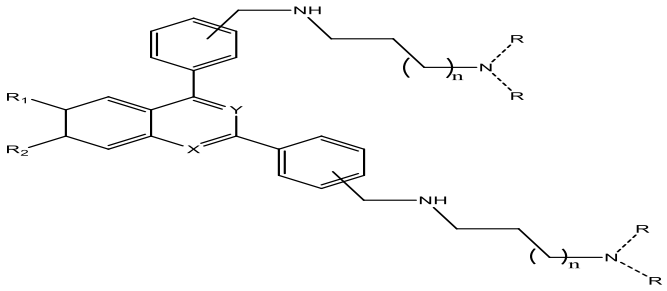
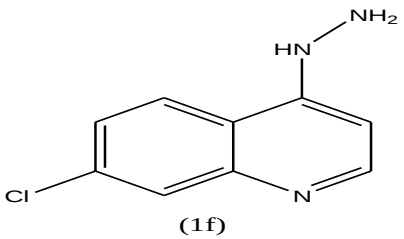


Fig no.19: quinoline compounds

Ten quinoline derivatives (fig no.20) are synthesized by Soares RR et al. 5 of which were joined to the sulphonamide group, and 5 to the hydrazide group. Hydrazide derivative named 1f showed action against the formation of blood parasites in vivo same as that of chloroquine [60].



(1f)

Fig no.20: quinoline derivatives having sulphonamide group, and 5 to the hydrazide group

Vlahov R et al. presented a method for synthesizing 6-amino-2,4-dimethyl quinoline compounds (fig no.21) by substitution at the C-5 and C-8 positions. The synthesized compounds have antimalarial properties. [61]

Four quinoline derivatives have been synthesized byKlingenstein R et al.One of the quinoline derivatives demonstrated very strong anti-malarial activity in vivo on Plasmodium berghei. Nand has more efficacy than chloroquine in vitro against a Plasmodium falciparum strain that is resistant to reference medication[62].

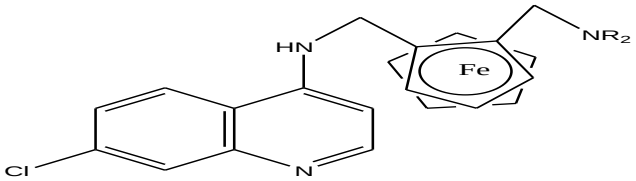


Fig no.21: 6-amino-2,4-dimethyl quinoline

2-quinolinylbenzocycloalcanones derivatives (fig no.22) were synthesized by harris JE et al. The results of these tests indicate that quinolinylbenzocycloalcanones have antimalarial action through a variety of pathways[63].

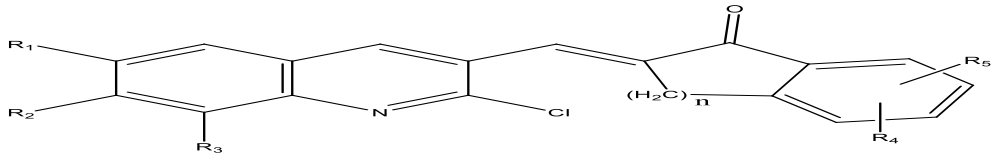


Fig no.22: -Quinolinylbenzocycloalcanones derivatives

Lobo GM et al. created some 2-quinolinylmethylidene-5,7-dimethoxyindanones and tested their effectiveness against malaria[64].

Bis-quinoline derivatives developed by Raynes et al., are effective against parasites that are both CQ-resistant and CQ-sensitive[65].

Modapa et al., synthesize ureido-4-quinolinamides (fig no.23), the compound showed antimalarial activity at MIC 0.25 mg/ml against a P. falciparum strain sensitive to chloroquine. [66]

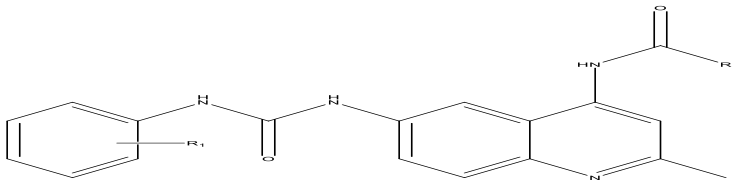


Fig no.23: Ureido-4-quinolinamides derivative

Against chloroquine-sensitive (fig no. 24) P. falciparum strains, Narayan AB et al. reported the production and significant antimalarial activity of several pyridine-quinoline-based analogues [67].

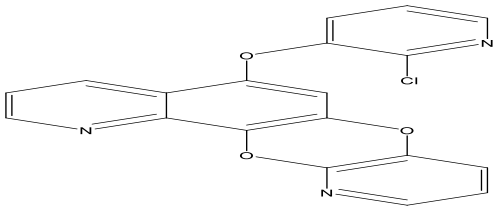


Fig no.24: Pyridine-quinoline-based analogues

Novel N-(7-chloroquinolin-4-yl)piperazine-1-carbothioamide and 1,3,5-triazine derivatives (fig no.25) were reported by Bhat et al. These hybrid conjugates exhibit potent antimalarial activity against both wild and mutant parasites after changing the substitution pattern[68].

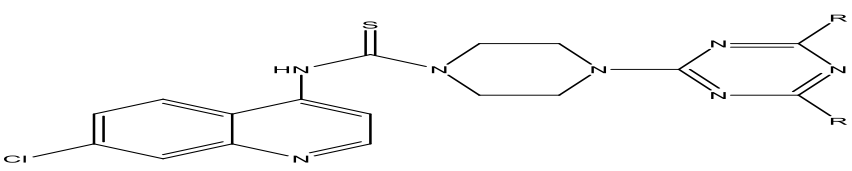


Fig no. 25: N-(7-chloroquinolin-4-yl)piperazine-1-carbothioamide and 1,3,5-triazine derivatives

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