Review on the synthesis of biologically active nitrogen heterocycles as potential anti-malarials

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The study of heterocyclic compounds has attracted the attention of chemists very earlier and continues ever, producing a plethora of new compounds. Moreover, heterocyclic compounds were not only attracting the attention of organic chemists but also pharmacists and biologists in view of their interesting pharmacological potentials. Among the heterocycles, nitrogen containing heterocyclic compounds such as indoles, benzo analog carbazoles, quinolines, its benzo-analog acridine are some of the important structural components in alkaloids and in many pharmaceutical agents. Vector control is a serious concern in developing countries, every year a large part of the population in the world is affected by one or more vector borne diseases, such as malaria, filaria, dengue etc., Malaria is life-threatening disease, predominant across 92 countries resulting in over a 3.4 billion people being infected annually; research to develop new antimalarial drugs have drastically increased over past 10 years. Quinoline derivatives such as Chloroquine, Mefloquine, Primaquine, Tafenoquine are widely used to fight against malaria. Chloroquine (CQ), the most widely used antimalarial drug, is an acidotropic agent which accumulates to high levels in malaria-infected erythrocytes.

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Malaria is a protozoan parasite belonging to the Plasmodium genus. Malaria is spread by plasmodium species that infect blood cells in mammals, birds, and reptiles. Despite efforts to eradicate malaria, the impact of global society continues to expand. Malaria is regarded as an illness that must be treated. The World Health Organization's Annual 2020 Malaria Report estimates that 229 million people were infected with malaria in 2019. When a mosquito bites them for a blood meal and the salivary glands carry malaria sporozoites, malaria is transmitted to humans. Sporozoites enter the human bloodstream through saliva and circulate until they reach the liver. Before becoming a single hepatocyte, each sporozoite travels through a number of hepatocytes in the liver. Antimalarials have only been studied in human pregnancy a few times. In essence, antimalarial medications have no pharmacokinetics, safety, or efficacy in pregnant women. A lack of data is the basis of malaria prevention and treatment advice during pregnancy. During pregnancy, the medicines used for malaria differ according to the quarter of your child.

The mechanism of action of Quinoline-based antimalarial medication entering red blood cells and combining it with Hemoglobin (hb) into food vacuoles has been reported (Arezoo Rafiee Parhizgar *et al*). Once the medicines have been completely mixed with Hb, Hb separates into amino acids and heme (ferriprotoporphyrin IX) as a byproduct. Hb breakdown requires a number of enzymes to be utilised. There is no enzyme needed to digest poisonous heme for plasmodium parasites, which causes

the parasite to die.In a range of ways, malaria parasites can become drug resistant. Transporter proteins, which promote medicine flux from the parasite, cause chloroquine resistance. The inhibitors of dihydrofolate target malaria parasite enzymes in the folate path. Resistance of the parasite attracted chemists to produce or modify antimalarial drugs.

The literature review resulted in a better understanding of the wide range of quinoline-based antimalarial drugs. This article discusses a unique process for synthesizing carbazole, which will be used to make quinoline analogues

A German pharmaceutical company discovered chloroquine in the 1940s.. After resynthesizing CQ, it was reported as the most potent drug to treat malaria in humans. It was soon widely produced and consumed. The bark of the South American cinchona tree has been known to possess antimalarial properties for at least 350 years. The active components are quinine, its diastereomer quinidine, and the active components of chloroquine. Despite the drug's widespread use, it took nearly 20 years for resistance to develop. Southeast Asia and South America were the origins of the two primary focal points of CQ resistance. CQ-resistant parasites like P.vivax and P.falciparum do not collect CQ efficiently in their feeding vacuoles. Furthermore, some recent investigations have found that parasites with point mutations in the gene encoding for the P.falciparum chloroquine resistance transporter (PfCRT)protein accumulate less CQ. Another mutation, S163R, is responsible for the strains' restoration of CQ sensitivity(Bayer *et al* 2011).

TDR30137, a commercially accessible chemical related to N-substituted carbazoles, has shown to be a success. An IC50 of 57 nM in human red blood cells has been shown to be present.. The anamine linked to the substituted carbazole via a floppy chain had key strong features. It was also reported that employing two of the reported chemicals, overall parasitemia may be reduced by more than 99 percent. Against the strains, the compounds had moderate to strong antiplasmodial activity. A decrease in potency was seen for compounds having aniline substituents. A privileged core was discovered to be dihalogenated carbazol.The World Health Organization (WHO) backed a number of initiatives to find novel chemical entities to combat malaria(Molette *et al* 2013). Ju deng compared Fischer-carbazole Borsche's synthesis with Kurti and co - workers where fischer synthesis is based on condensation, cyclization, and dehydrogenation sequences of acidic and Oxidative conditions using aryl hydrazines and cyclohexanones. In this work, aniline, which is an easily available starting material, is reacted with methyl cyclo hexanone.Substituted aniline reacts with methyl cyclohexanone in presence of KI/I2. Different yields (JuDeng *et al* 2017). Plasmodium falciparum (Pf), a protozoan parasite, causes malaria. Hsp90 is an important and highly conserved protein in all eukaryotes. Because PfHsp90 amino alcohol carbazole (N-CBZ) inhibits the parasite's life cycle, it is both an antimalarial and an antiparasitic. During the stage of red blood cells Molecular dynamics and docking studies, as well as a few other experiments, are performed on N-CBZ molecules(Picard *et al* 2016). Recent research shows that carbazole compounds are extremely active for a wide range of species Carbazole compounds have shown promise as multifunctional medications for the treatment of neurological conditions. Through a variety of methods, they have anticancer and antimalarial activities against a range of cell types (Gluszynska *et al* 2015).

The strong and affordable 4-aminoquinoline medication CQ, as well as several similar medicines,

resulted through systematic modification of quinine. Chloroquine, amodiaquine, Primaquine And piperaquine are the four types of aminoquinolines. Primaquine is an eight-aminoquinoline anti hypnozoite compound. It has been reported on the role of several moieties attached in the place of the 7-chloro group. .CQ-resistant P. falciparum strains showed effective reduction of carbon-side chain by 2-3 atoms or lengthening it by 10-12 atoms. The connection between structure and business, Studies on 4-aminoquinoline antipalinium compounds reveal the requirement for antimalarial activities for the 7-chloro-4-aminoquinoline nucleus. Hematin synthesis inhibition and drug accumulation are two of the major activities of the drug. The 4-aminoquinoline products of the thiazolidin-4.ones/[1,3]thiazinan-4-one 2-substitute were synthesised at room temperature using the proper amine and aldehyde replaced by DCC in the presence of anhydrous THF(Solomon *et al* 2007). Since 1948, amodiaquine (AQ) has been present on the market. AQ as a "Artemisinin Combination Therapy (ACT)" for uncomplicated malaria has been named by the World Health Organization (WHO) which makes it a major medicine. AQ is Plasmodium falciparum's most effective treatment. Many ACTs in Africa have been identified as fraudulent. Green chemistry technology, particularly in sub-Saharan Africa, has not been realised for the production of pharmaceuticals which is economically viable(Jones *et al* 1948). In the 1960s, piperaquine was synthesised. In the regions of China and Indochina it was commonly used as a prophylaxis and treatment. The art of artemisinin derivatives unfortunately came into being in the 1980s when the piperaquine-resistant strains developed. Piperaquine has been found to be one of several compounds in combination with a derivative artemisinin in the following decade. This approach has now been backed by the World Health Organisation (Davis *et al* 2005).

Hybrid 4-aminoquinoline derivatives, 1,3,5-triazine were synthesized by Bhat et al. Their chemical structure was tested with a spectrometric analysis of 1H-NMR, 13C-NMR and the FT-IR. The antipalmic activity of these compounds against chloroquine (3D-7) and chloroquine resistant P. falciparum strains was tested in vitro (RKL-2). Refluxing 1,2,4,6-trichloro-mono-substituted 1,2,4 and 7-chloro-N-(2-(piperazin-1-yl)ethyl)quinolin4-amine in 1,4 dioxane synthesis the desired compounds(Bhat *et al* 2012). Nine new derivatives of 7-chloro-4-aminoquinoline, derived from (Casagrande *et al* 2012) They have been tested against plasmodium falciparum for their malaria activity. There was an excellent compound against chloroquine for antimalarial activity. (Shashi Pandey *et al* 2013)summarised a number of novel 4-aminoquinoline tetrazole derivatives. Compounds have been summarised through two simple steps. The target compound was obtained by reacting with aldehyde and isocyanide intermediate compounds in the presence of MeOH TMSN3.(Ashok *et al* 2010)synthesised modified 4-aminoquinolines derivatives and quinoline – acridine hybrids. Two compounds showed excellent antimalarial properties.The new 21 heterocyclic chloroquine hybrids containing either the benzylamino fragment or the N-(aminoalkyl)thiazolidin-4-one mode were synthesised by (Rojas *et al* 2011). Two compounds have shown CQ-like IC50 values.(aminoquinoline products) The radical cure of recurring vivax malaria is made with primaquine. It is an antimalarial medicine that kills P.vivax, P. falciparum and P. malaria in the main exoerythrocytic stages. It kills or inhibits the growth and development of gametocytes of all species in the mosquito field. It does not have a major effect on other erythrocytic stadiums and should therefore not be used alone.

Many scientists and researchers are showing interest in the synthesis of carbazole because many carbazole derivatives show biological and pharmacological activities like anti-cancer anti-malarial etc. Therefore, our aim is to synthesize 1- oxo carbazole from which we will synthesize quinoline and carbazole (fused compound). Our Potential precursor for deriving anti-malarial target is carbazole because it plays a vital role in pharma activities. To synthesize carbazole many methods can be adapted but, in our work, we are taking aniline as starting material. For the exploration of chemistry in carbazole structure we are synthesizing carbazole instead of direct procurement of carbazole. Aniline on diazotization gives diazonium salt. We can also use derivatives of aniline for the synthesis. Cyclohexanone on reacting ethyl formate in basic condition (sodium methoxide and diethyl ether) on mixing we get 2-hydroxymethylene cyclohexanone. By reacting with 2-hydroxymethylene cyclohexanone with diazonium salt in presence of sodium acetate and methanol we get respective hydrazone derivatives. Substituting hydrazone on reacting with Kent's reagent (acetic acid and hydrochloric acid) and refluxing it we get 1-oxo carbazole. 1- oxo carbazole on reacting with hydroxyl amine in presence of pyridine give oximes. Oximes are good reagents to synthesize nitrogen heterocyclic derivatives which are pharmacological activity and it plays a vital role in drug discovery. Refluxing 1-oxo carbazole in presence of Pd/C and diphenyl ether we get 1- hydroxy carbazole.

Among the pyrano carbazole alkaloids, 2,2-dimethyl-2*H*- pyrano carbazole alkaloids, girinimbine was one of the compounds isolated from *M. Koenigii* Spreng. The isolation of these classes of compounds becomes an active area of study since these compounds possess high level of biological and pharmacological applications. The isolation of these compounds was widely reported in literature with multiple steps with very low yields. While synthesis pyrano carbazoles produced multiple by-products which were major drawbacks. Therefore, we used a different approach to pyrano carbazole and its derivatives.

Sridharan and his co-workers synthesized 2,2-dimethyl-2,3-dihydropyrano[2,3-*a*]carbazol-4(11*H*)-ones in high yields using 3,3-dimethylacrylic acid with trifluoroacetic acid at room temperature. The generality of this reaction using many substituted carbazole derivatives and all the cases it gave us promising results. We have to verify the structure of pyrano carbazole using IR spectroscopy, NMR and X-ray Crystallography.

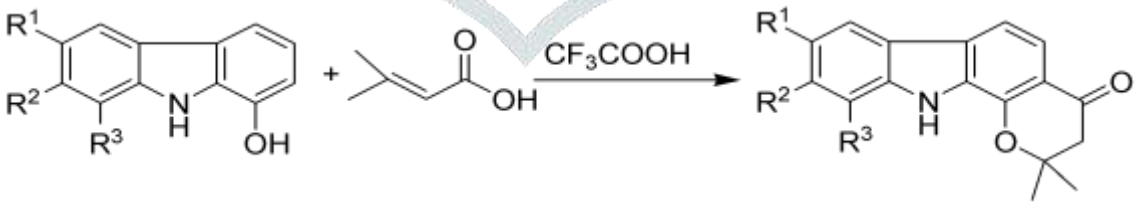

Figure 3.6 Reaction of 1-hydroxy carbazole (1) with 3,3-dimethylacrylic acid in trifluoroacetic acid

Literatures reported that synthesis of 2-methyl- and 2-phenyl-pyrano [2,3-*a*]carbazol-4-ones and their substituted derivatives, but most of the procedures suffer from limitations such as multiple steps, low yields or difficulty in accessing the starting materials. These demerits prohibit adoption to large scale manufacturing of pyranopyrazoles in acceptable quantities needed for pharmaceutical as well as biological applications. Hence an attempt was made to synthesize phenyl pyranocarbazolones from easily accessible 1-hydroxy carbazoles and in a single step procedure.

The synthesized 2,2-dimethyl-2,3-dihydropyrano[2,3-*a*]carbazol-4(11*H*)-ones was used as an efficient candidate to develop many substituted pyrano carbazole derivatives. In general, quinoline compounds possess high level of anti-malarial applications and hence we want to combine quinoline and 2,2-dimethyl-2,3-dihydropyrano[2,3-*a*]carbazol-4(11*H*)-ones in an anticipation to explore the biological and pharmacological properties. Along with the anti-malarial drug, an attempt has been made to develop 2-aryl-pyrano[2,3-*a*]carbazol-4-ones,4-aryl-pyrano[2,3-*a*]carbazol-2-ones,3-hydroxy-2-aryl-pyrano[2,3-*a*]carbazol-4-ones and related compounds using the easily accessible 1-hydroxycarbazoles and 2-cinnamoyl-1-hydroxycarbazoles and were reported by Sridharan and KJR Prasad. We are in the process of developing new avenues of malarial drugs by combing the carbazole and quinoline moieties. We expect the synthesized derivatives will yield us promising results.

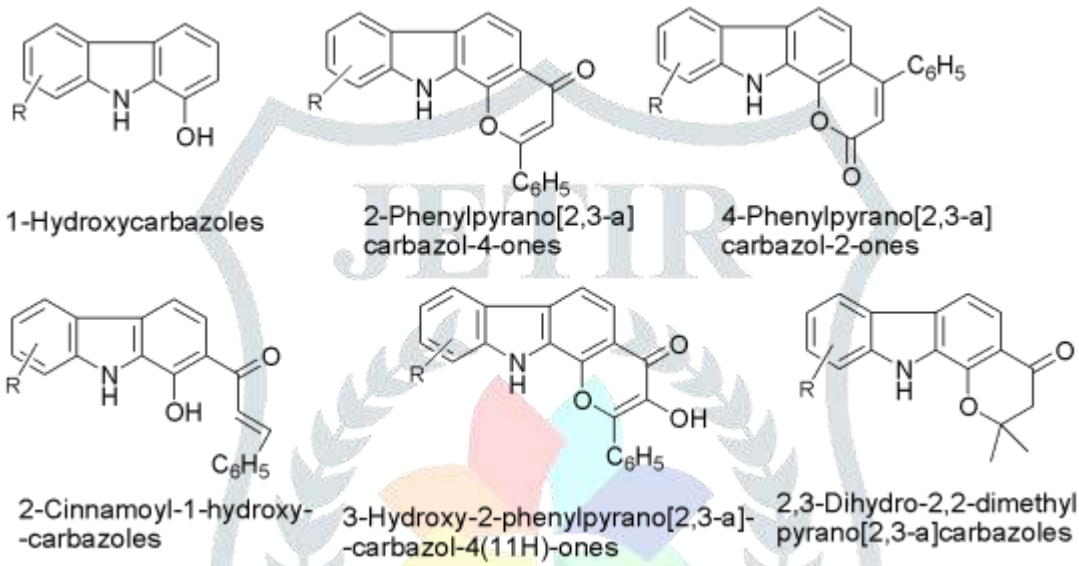

figure 4.1 Biogenetically possible pyrano derivatives using the easily accessible 1-hydroxycarbazoles and 2-cinnamoyl-1-hydroxycarbazoles

Quinolines and quinolones, which come from plants, animals, and microbes, have long been known to have antibacterial, insecticidal, anti-inflammatory, and anti-tumor properties. In the field of drug discovery, quinoline has been utilised as a powerful scaffold. It paves the way for new semi-synthetic or synthetic molecules to be synthesised in a variety of ways. Following a thorough review of the literature, it is clear that quinoline-based hybrid compounds with antimalarial activity are cost-effective and have a lower risk of drug-drug interactions. Efficacy, safety, availability, cost, and acceptability are all prerequisite properties for a medicine. With the information obtained and presented in the paper, we are optimistic that we will be able to achieve all of the requirements, resulting in a strong antimalarial medicine.

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