How to Cite:
Mishra, P., Kumar, A., Sharma, U. C., Saxena, A., Prabahar, A. E., Gupta, S., & Verma, A. K. (2022). Quinoline derivative and their pharmacological & medicinal potential. *International Journal of Health Sciences*, *6*(S3), 2016–2040. https://doi.org/10.53730/ijhs.v6nS3.5918

Quinoline derivative and their pharmacological & medicinal potential

Preeti Mishra
Raja Balwant Singh Engineering Technical campus, Faculty of Pharmacy Bichpuri, Agra

Avinash Kumar
M.pharma scholar Department of Pharmacy, MJP Rohilkhand University Bareilly

Umesh Chand Sharma
Raja Balwant Singh Engineering Technical campus, Faculty of Pharmacy Bichpuri, Agra

Ankit Saxena
M. pharma scholar, Department of Pharmacy, MJP Rohilkhand University Bareilly

Dr. A. Elphine Prabahar
Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad

Sushmita Gupta
Department of Applied Chemistry, MJP Rohilkhand University, Bareilly

Amit Kumar Verma
Faculty, Deptartment of pharmacy MJP Rohilkhand University Bareilly

***Abstract*---**The review article titled as "Quinolines" is basically designed with the aim of approaching the precious properties that the compound is entitled to possess. It is a heterocyclic compound possessing varied form of biological as well as pharmacological activity. This article basically focusses on the characteristics possessed by the compound of Quinoline. It tends to decipher a useful amount of information regarding the biological properties of the compound and its utilization in the development of various medications. The information provided in this article can be proved as a useful instrument for the various research scholars who are focusing their target of research with respect to Quinolines .It provides all the general information the quinolines and also throw light on the

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
***Corresponding author**: Verma, A. K.; Email: professoramitmjpuniversity@gmail.com*
Manuscript submitted: 18 Nov 2021, Manuscript revised: 09 Feb 2022, Accepted for publication: 27 March 2022

numerous therapeutic properties being possessed by the compound, that plays a prominent role in the treatment of various ailments.

***Keywords*---**quinolines, heterocyclic, anti-malarial, electrophile, chloroquine, amodiaquine.

Introduction

Nitrogen containing aromatic heterocyclic compounds are termed as quinolines. These are also referred as 1-aza-napthlene as well as benzo-pyridine. Quinoline is entitled as a weak tertiary base. It tends to form salt with the aid of acids and owe to decipher various chemical reactions that resemble to some of those of pyridine and benzene. It tends to depict two types of reactions i.e, electrophilic as well substitution reaction of nucleophile. As an oral medication it is beneficial to humans with no adverse reactions. It is also utilized as inhalational medication. These compounds possessing quinoline nucleus are obtained from various natural herbal sources of plant. Such as cinchona alkaloids, it tends to owe a significant pharmacological as well as enhanced biological activity. Quinolines are found to play a prominent role as an anti-malarial agents. It is also employed as anti-inflammatory agent, as anti-bacterial, as anti-fungal etc. It also exhibit analgesic property.[1]

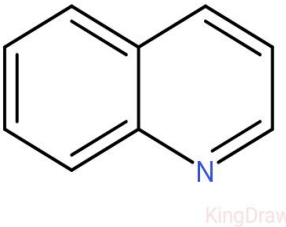


Fig: Quinoline

IUPAC NAME.[2] **:** 1-Benzopyridine

- Benzo[b]pyridine
- 2-Azabicyclo[4.4.0]deca-1(6),2,4,7,9-pentaene

Classification of quinolines

First generation of the drugs comprises of the following:

- Cinoxacin
- Flumequine
- Nalidixic acid
- Oxolinic acid
- Piromidic acid
- Pipemidic acid
- Rosoxacin

Second generation of the drugs comprises of the following:

- Ciprofloxacin
- Enoxacin
- Fleroxacin
- Lomefloxacin
- Ofloxacin
- Pefloxacin

Third generation of the drugs comprises of the following:

- Balofloxacin
- Grepafloxacin
- Levofloxacin
- Sparfloxacin

Fourth generation of the drugs comprises of the following:

- Gatifloxacin
- Clinafloxacin
- Moxifloxacin
- Prulifloxacin
- Etc

Synthesis [6]

There are various methods established for the synthesis of quinolines. Some of the them are like Skraup Doebner-Von Miller, Pfitzinger, Friedlander, Conrad-Limpach and Combes synthesis.

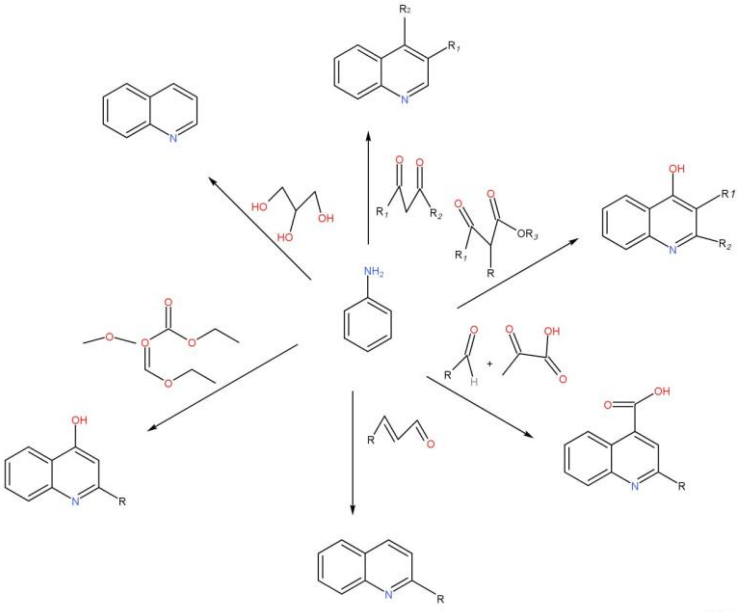
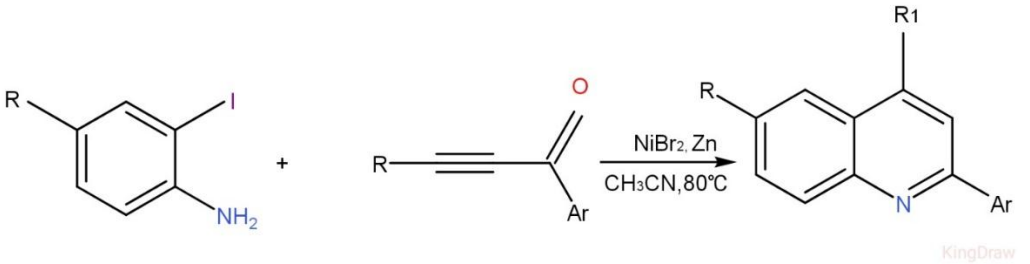


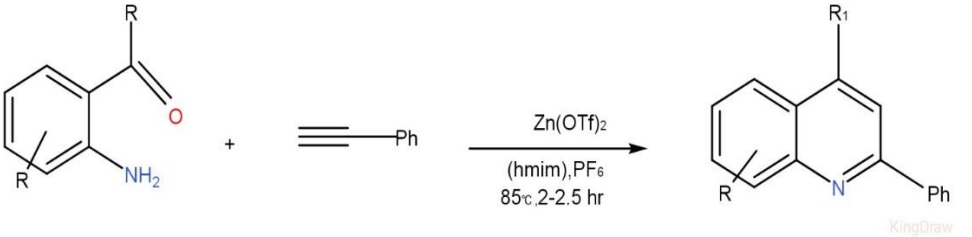
Fig: synthetic approaches

Synthetic approaches

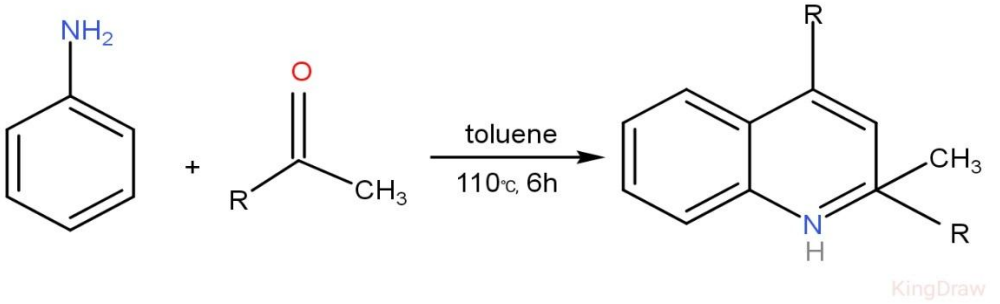
Various research scholars have proposed various synthesis like a scholar proposed the synthesis of 2,4-disubstituted quinolines with the involvement of condensation of 2-iodoanilines with the utilization of alkynyl aryl ketones by employing nickel as catalyst.



These 2,4-Disubstituted quinolines are obtained by the cyclization of 2-aminoaryl ketones with the involvement of phenylacetylenes. The medium of this reaction is ionic liquid that is carried out in the presence of catalytic measure of indium(III)trifluoromethanesulfonate under microwave as well as solvent free conditions.

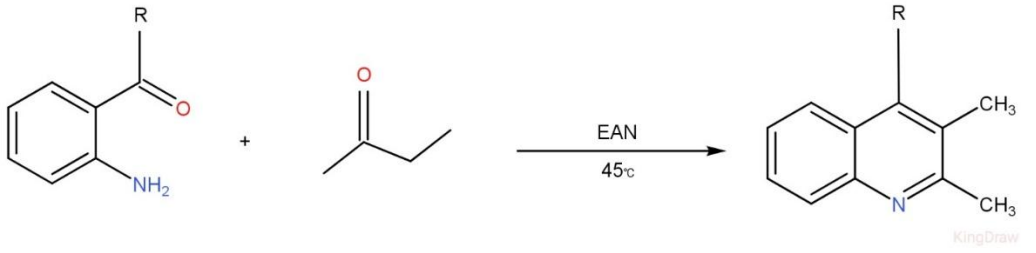


2,4-Diphenyl-2-methyl-1,2-dihydroquinoline obtained by the condensation and then proceeding with the cyclization process by the utilization of aniline and acetophenone. This reaction tends to be completed in the presence of catalyst i.e, zeolite.

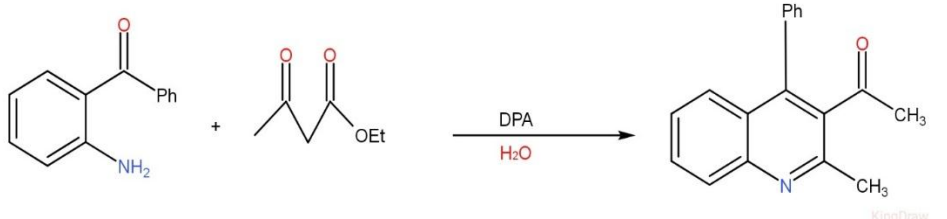


The 2,3,4-Trisubstituted quinolines are synthesized by the employment of Friedlander annulation of 2-amino reactions by substitution f aromatic ketones. As well as reactive methylene group that contains a carbonyl compound in the residence of ethyl-ammonimu-nitrate.

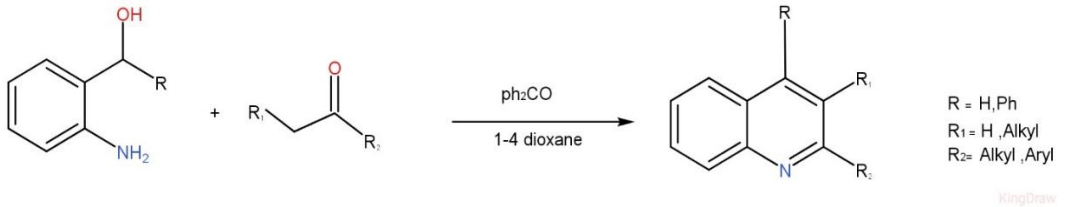
2020



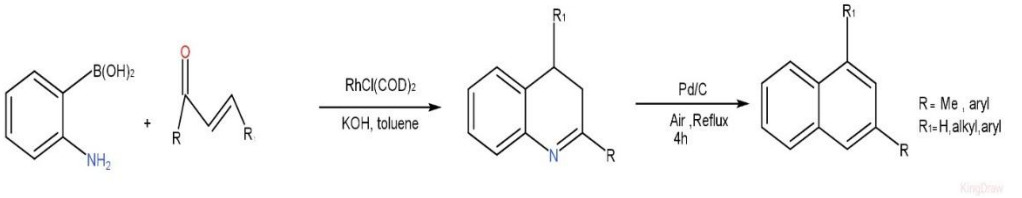
By agitating 2-aminoaryl ketones with several alpha methylene ketones by the utilization of dodecylphosphonic acid as a catalyst, deprive of solvent presence. This results in the synthesis of poly:substituted quino-lines.



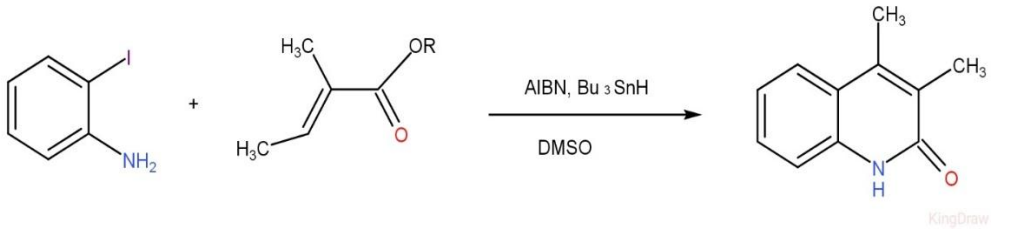
The reaction of 2-aminobenzyl alcohol with ketones or with alcohols in the reaction catalysed by base and results in the production of polysubstituted, quino-lones, in this reaction benzophenone acts as a scavenger of hydride.



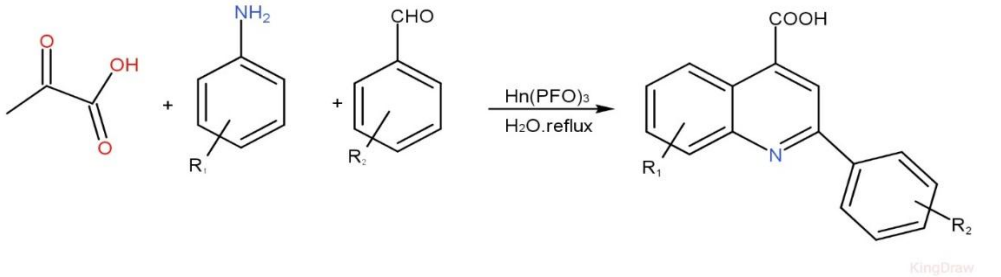
Another research scholar establish the synthesis of quinolines with the aid of alpha-beta unsaturated ketones and aminophenylboronic acid derivatives. This method is also regarded as upgraded version of Skraup-Doebner-Von-Miller synthesis, and this reaction is carried out in the presence of a base.



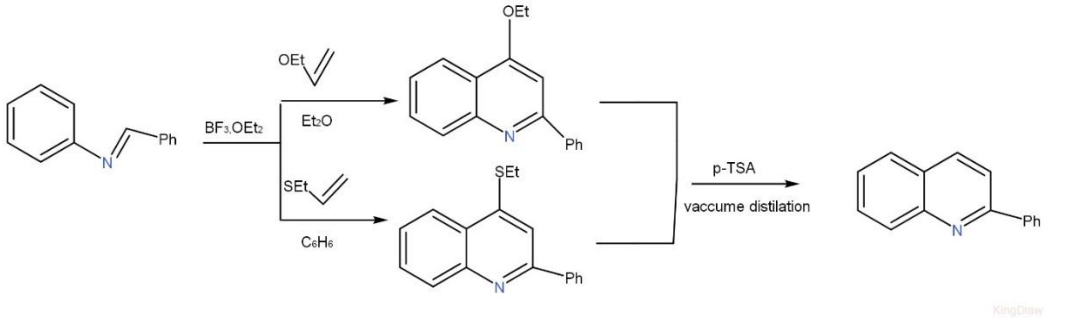
The 3,4-Dihydroquinoline-2-ones is found to be synthesized by the involvement of 2-iodoanilines and several acrylates by utilizing azobisisobutyronitrile by employing tributylin hydride as a catalyst.



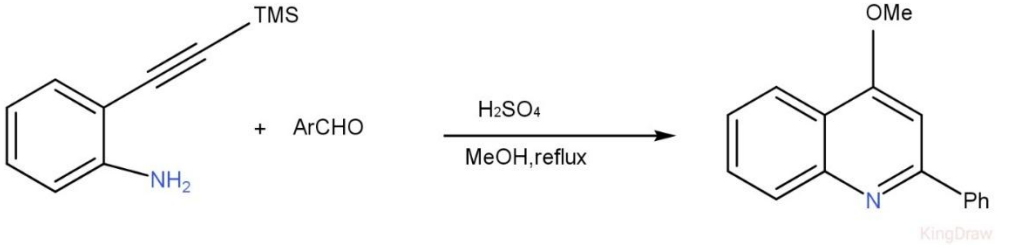
Another research scholar also establishes his synthetic approach for quinolines by employing 2-phenylquinoline-4-carboxylic acid and treating it with pruvic acid and substituted by aniline as well as benzaldehyde by involving rare earth metals as catalyst and this requires water under the reflux conditions.



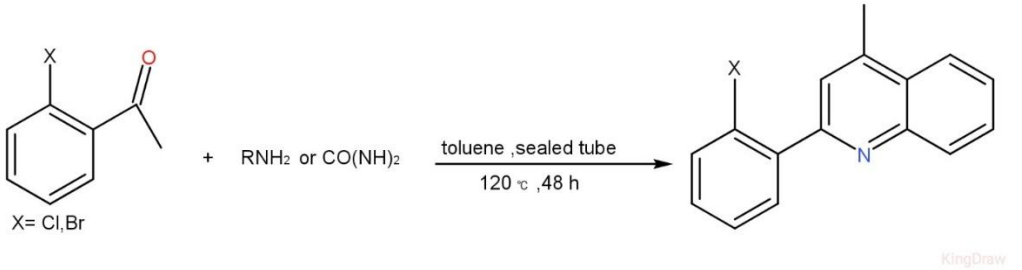
Another scholar reports the synthesis of quinolines substituted with phenyl and by reacting it with ethyl vinyl ether in acid catalyst environment by aiding boron trifluorde etherate.



Another report decipher the synthetic approach for 2-phenyl-4-alkoxy quinolines, by employing cyclo-condensation of 2-(2-trimethylsilyl)ethynyl)aniline by using aromatic aldehydes in the existence of sulphuric-acid in the methanol solvent.

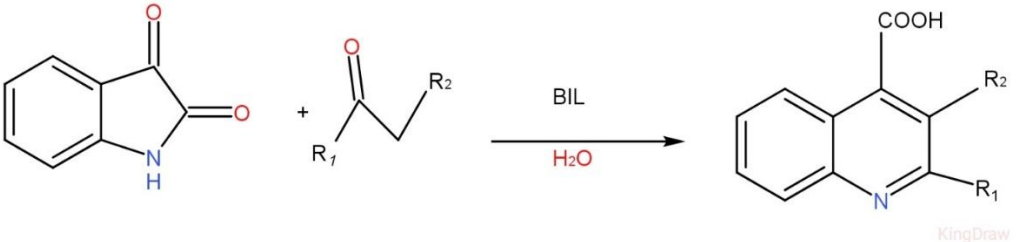


When 2 mole-cules of haloacetophenones are condensed with urea or primary aminestends to yield quinolines that are substituted with halogens. These are formed due to the cleavage.

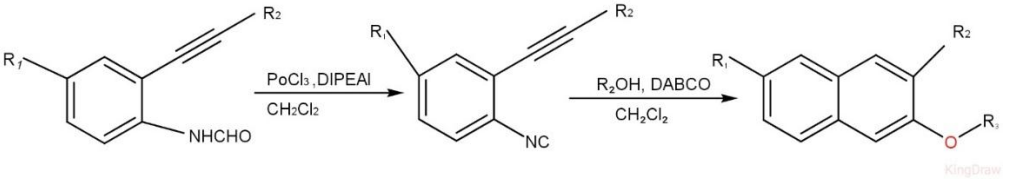


Another research scholar establish certain other synthetic approaches like treating isatin with aryl-methyl ketones in the existence of ionic-liq that are basic in nature. This reaction is carried out under green-ultrasound conditions of synthesis. The benefits of utilization of this method are:

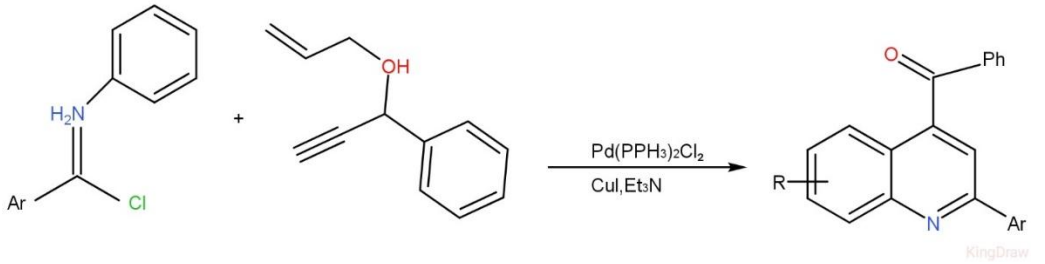
- Is visualized as a a green method.
- It tends for Higher yield.
- It possess high Selectivity.
- Shorter span of time.



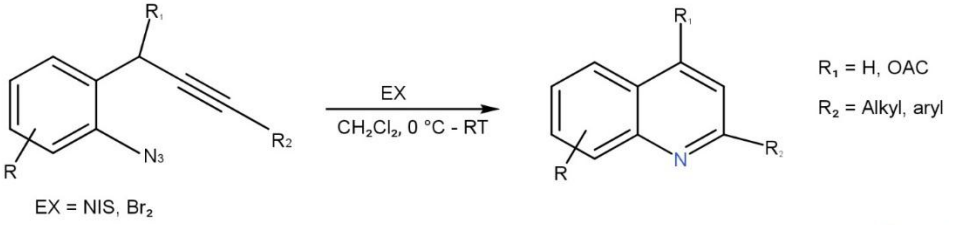
The synthesis of the compound 1,4-Diazabicyclo[2.2.2]octane by utilization of alkyl-vinylaryl iso-cyanides under the presence of alcohols and phenols. The reaction is competed by the involvement of electrophilic reaction.



When benzi-midoyl chloride tends to treat with a intermediate results in the formation of various derivatives of quinolines.



Various diversed form of quinolines tend to react with 1-azido-2-(2-propynl) benzenes by the involvement of electrophilic agents by employing cyclo-condensation process.



Mechanism Of action of quinolines.[4]

The mechanism of Quinolines is by targeting the reticence of the pursuit of two important enzymes that are DNA-gyrase and Topo-isomerase-IV, that deals with the refashioning of the super-coiling of the chromosomes which is basically needed for the synthetic purpose of DNA, the process of transcription as well as division of cell process. These enzymes tend to reform DNA topography by passing it with an intact double-helix through a transient 4-bp lurch double-stranded smash that they tend to introduce in a discrete chunk. With a aim to protect its genomic integrity at the time of the process. DNA-gyrase and topoisomerase-IV tends to form covalent bonds in between the most-active site of tyrosine remanants that stick-out at the DNA disjuncture, that forms the cleavage of enzyme with DNA complexes that are referred as complexes of cleavage. Quinolones tends to interrupt with this censorious activity by binding in a reverse way to enhance the process of cleavage of complexes at the enzyme–DNA involving cleavage–ligation active site, that decipher the increased unvarying-state congreation of cleavage-complexes by physically inhibiting DNA strand-ligation. Quinolone's topoisomerase binding capacity that was signified through a water–metal ion bridge, in which a non-catalytic magnesium-ions tends to co-ordinate with 4 water molecules that owe to form a bridge for hydrogen-bonding betwixt the quinolone and the serine and the acidic left over that tend to act as initiator for the enzyme DNA-gyrase as well as topoisomerase-IV. In spite of their extensive functional and structural corresepondance, DNA-gyrase and topoisomerase-IV that possess varied physiological corporal functions. DNA-gyrase is found to generate the energy by opting for the hydrolysis of ATP to energetically incorporate negative supercoils into DNA that are basically beneficial for various purposes, such as:

- Establishing the super-helical bulk-density that permits the condensation of the chromosomes.
- Deciphering the rate of torsional tautness that stock-pile in vanguard of replicating-forks and complexes of transcription.
- Encouraging the melting locally for the processof transcripation that is basically initiated by the enzyme RNA polymerase.

Topoisomerase IV decipher a significant role in preserving the chromosomal super-helical density and enhancing torsional stress, however it is entitled to a minute level whereas DNA- gyrase persue to emit positive supercoils and lacks the ability to incorporate supplementary gloom-ridden supercoiling of .Quinolones is regarded as target DNA-gyrase and the enzyme topoisomerase-IV that tends to possess varying potency in several different species of bacteria. Generally, DNA gyrase is regarded as the most prominent target of quinolones in Gram-negative species and topo-isomerase-IV the chief target in Gram-positive species. However, this has been staggered as to be invalid in certain instances, the example can be considered of Gram-positive species in which the enzyme. DNA gyrase is the most important centre for quinolones as well as various instances of being varied structure of quinolones that owe a clear chief aim within the same species or quinolones with somewhat same efficacy against opposed to both the enzymes.

Resistance depicted by Quinolines.[4]

The Quinolines tends to decipher the resistance basically indicated by three mechanisms. These mechanisms are illustrated below:

- Mutations related to chromosomes that play a key role in targeting the enzymes as well as their affinity which is related with the drug binding potency.
- It indicates the mutation of chromosomes that exhibit that the accumulation of drug is certainly reduced due to slight-increase or slight-decrease in the efflux potency.
- This is represented by the resistance acquired due to plasmid, that tends to target protecting proteins.

Biological activities

Quinolines are found to exhibit a wide variety of biological activity as well as pharmacological activity. These activities are briefly described below, these are as follows:

Anti-bacterial Activity Of Quinolines.[5]

The anti-bacterial activity is basically studied by employing the broth-dilution method.

Broth-dilution Method

This activity was established by elaborating and testing of various species of gram-positive bacterium, these species are:

- Bacillus subtilis
- Salmonella typhi
- Vibrio chlorea
- Escherichia coli

The inoculum was then prepared and the turbidity was determined and compared using the turbidimetric method.

Anti-fungal Activity of Quinolines.[5]

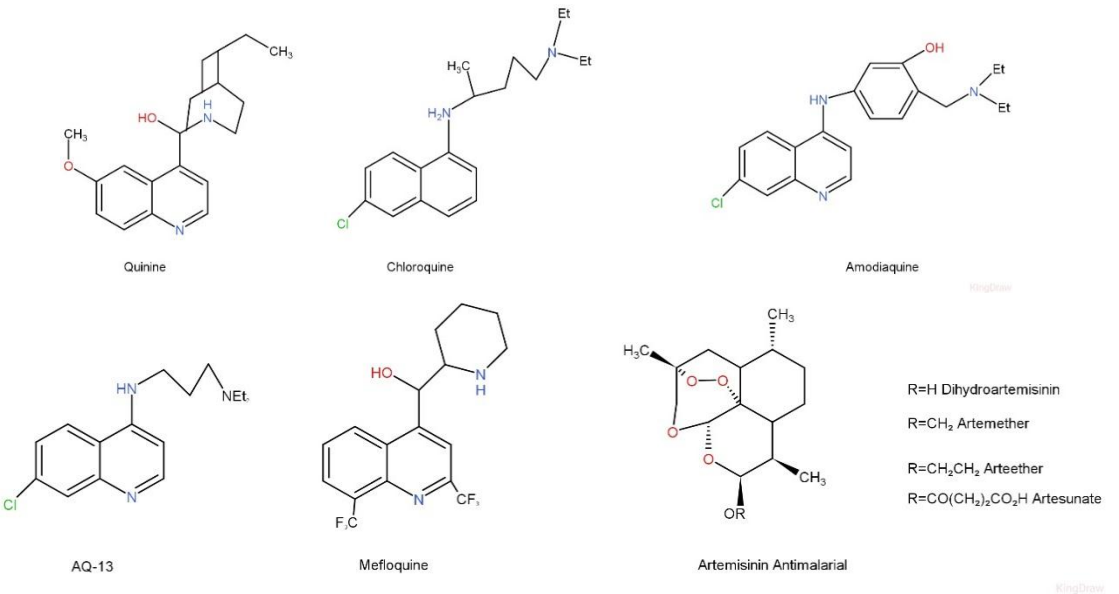
Quinolines are found to exhibit a wide range of anti-fungal activity and these are effectively utilised as a anti-fungal agent in the mitigation of various severe ailments that are confined to the infection caused by fungus.

Anti-Oxidant Activity Of Quinolines.[5]

These quinolines are found to possess a greater extent of Anti-Oxidant activity that contributes a lot to its effectivess as a agent that tend to posess a greater extent of anti-oxidant activity. It is determined using the scavenging method. In this method 1ml of methanolic solution was taken and added to the sample solution. Then these were kept for incubation at room temperature in dark environment for a time atleast thirty minutes and their absorbance was determined by using U-V spectrophotometer. This activity is basically due to their ability to donating hydrogen at a very rapid pace.

Anti-malarial Activity Of Quinolines.[6]

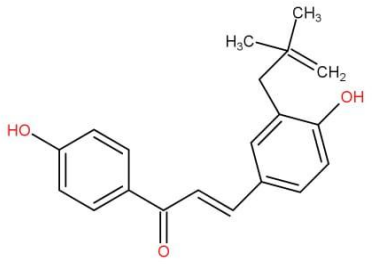
The ailment of malaria is often regarded as the one of the most widely spreading disease in the world. Estimation by WHO reveals that about more than forty percent of the population is under the threat of malaria and it results in death of large number of population as per the data recorded. Malaria is basically caused by a protozoal plasmodium which comprises of species of plasmodium falciparum, malariae, and ovale. This is often regarded as the most virulent parasite that infects humans. The problem of malaria founds to be alleviated at a very rapid pace as well as the problem of increased resistance is procuring at a large level. Regular attempts are being carried out in developing the vaccine for this ongoing ailment regarded as malaria although various others optional treatments are available, that tends to play a significant role in the eradication of malaria. The compounds possessing quinoline nucleus are found to be effective in the mitigation of the ailment of malaria, which is often regarded as a dreadful disease.

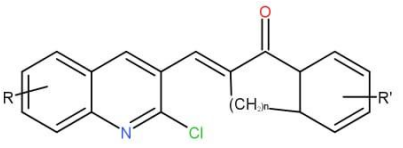


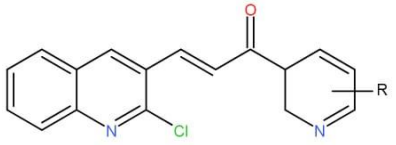
The above figures represent the chemical structure of some antimalarial drugs that are extensively used in the treatment of malaria and its prevention.

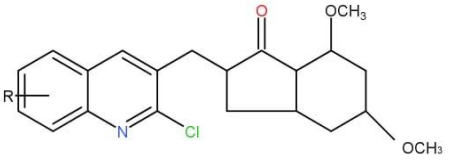
Quinoline Derived Chalcones

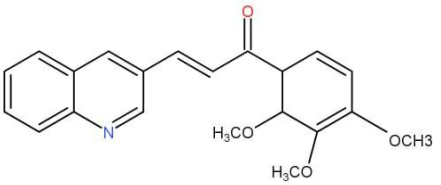
As we deal with chalcones one comes to know that it also possess a significant anti-malarial activity which was firstly reported from the isolation of Chinese root of liquorice plant, which possess a active constituent responsible for the anti-malarial activity, it is of natural source. As the time passes it was revealed that the anti-malarial activity was basically due to the presence of alkoxylated chalocones that possess polar rings usually that are substituted with a group possessing the electron-withdrawing potency as well as having the quinoline nucleus in their structure. After that a number of derivatives of chalcones owing quinoline nucleus were synthesized and their pharmacological potency was estimated and determined.





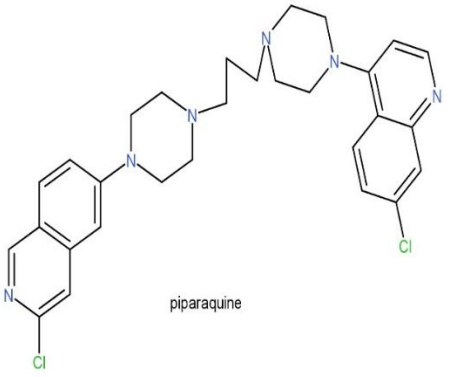




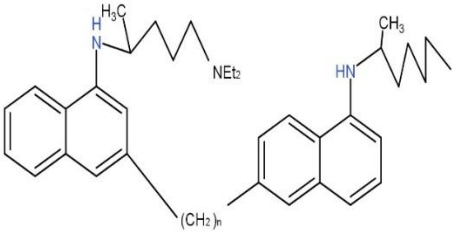


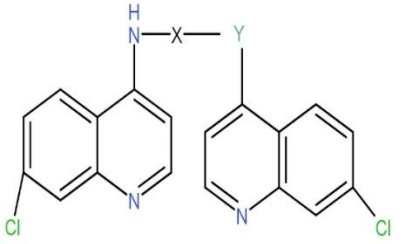
Derivatives of Bisquinolines

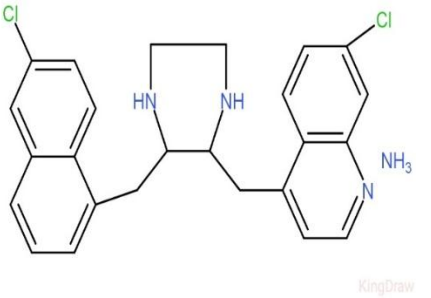
For the very first time compounds possessing bisquinoline was firstly synthesized during 1960 era and in china it was employed as a prophylactic as well as also employed for the mitigation of malaria at that point of time. But it came to decline due to the production of various other piperaquine resistant derivatives. Now again this category of drug is again focussed and is focussed on its production of more anti-malarial agents that possess bisquinoline nucleus in their chemical structure.



piparaquine



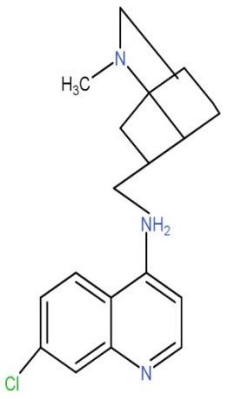


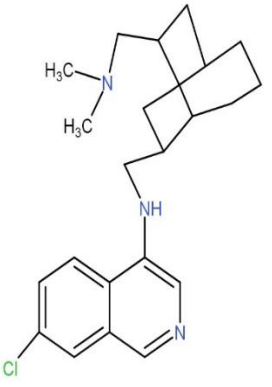


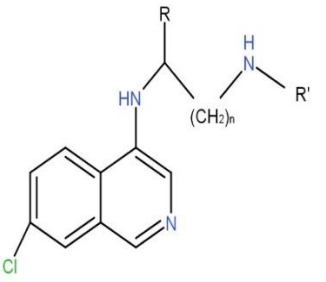
Various derivatives possessing bisquinoline nucleus are represented ain the above figures. All these derivatives are found to exhibit a wide range of anti-malarial efficacy as well as their potency is also high. They are also contributing a significant role in this programme of eradication of this dreadful disease of malaria. This ailment of malaria is found to pose a great threat of population with is widespread expulsion.

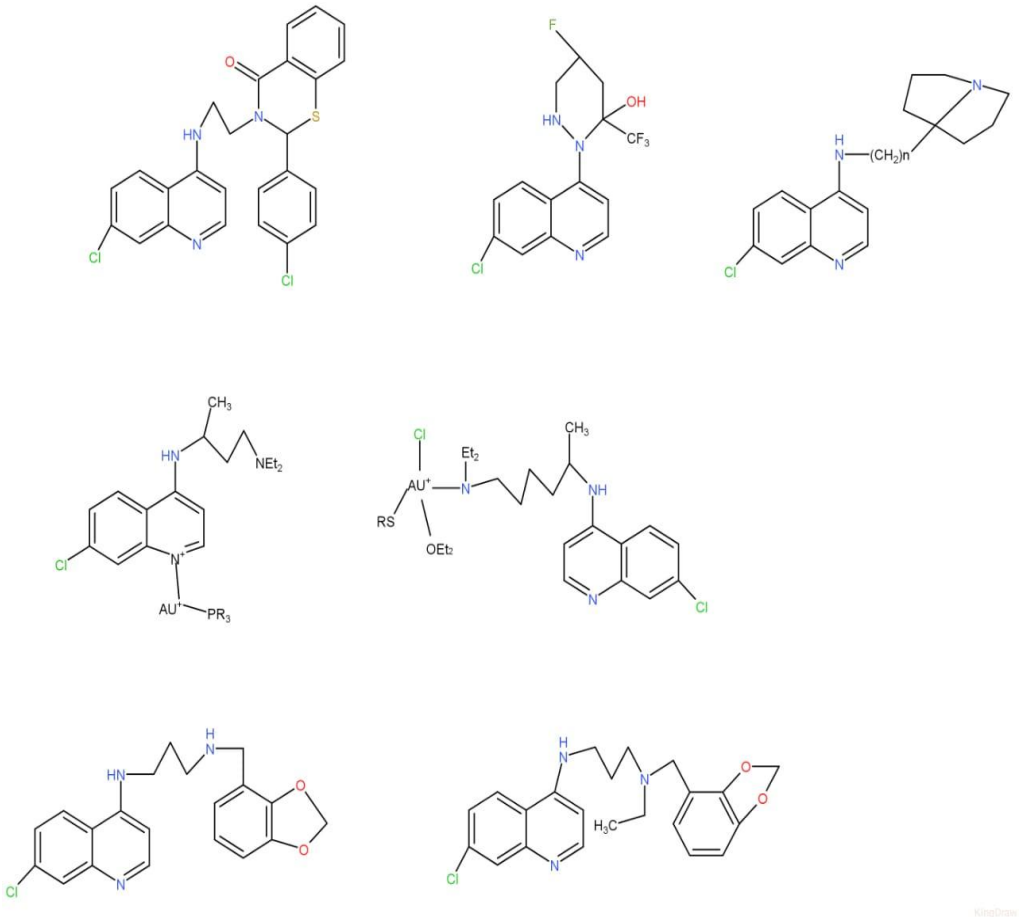
Chloroquine analogs derivatives

During the era of world-war II , the government of U.S play a significant role in sponsoring this as a anti-malarial drug and it tend to pose a great therapeutic value as an antimalarial medication. It was again introduced for clinical-practice during 1947. Various chloroquine derivatives are represented below which are effectively utilised in the treatment of malaria. These are also found greatly contributing to the list of anti-malarial drugs. Some of chemical structures of these chloroqunine derived structures are given below. These are as follows:



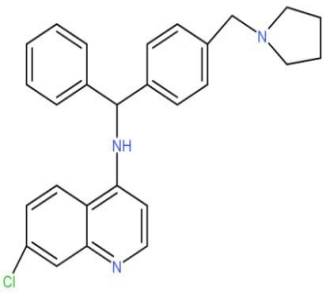


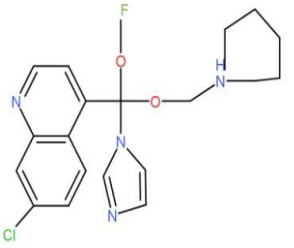


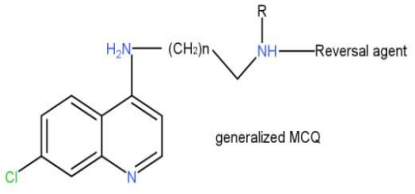


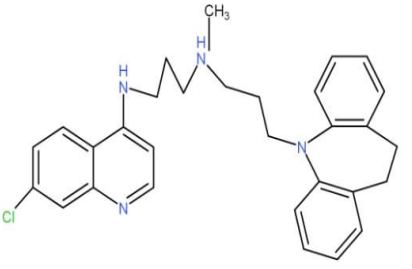
The process of designing as well as the synthetic approach of several anti-malarial drugs that are based on their chief structural pharmacophores, this approach has also become much prominent in the development of several anti-malarial drugs. This technique of designing antimalarials by utilizing their pharmacophores that is tend to be polyaromatic was firstly innovatively-designed by Gemma by employing the hybrid molecules possessing a pharmacophore similar to that of the clotrimazole. These intermediates found to be interacting and interfering with the metabolism process of plasmodium falciparum protozoa. This was possible basically due to the combining of the system of poly-aryl-methyl that tends to stimulate the stabilization of the intermediates derived from radicals. These also possess a diversified form of chemical structures and is utilized in various research work of several scholars who are focussing their interest in the development of several other medication of malaria. As malaria is a disease that is exploded at a fast rate so it requires more and more new formulations, as the problem of development of resistance is also at a pace, so it is also became a factor in focussing on more n more new medications with reduced adverse drug reactions as well as certain other chemical, physical and therapeutic interactions. These interactions tend to interefere a lot with the functioning of the medication and results in various complications. Some of the structures of derivatives of the

chloroquine which posess quinoline nucleus in their structure are given below. The structure of some of them is illustrated below:

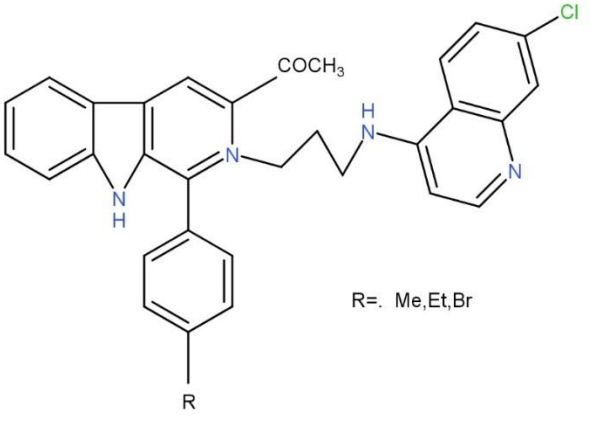


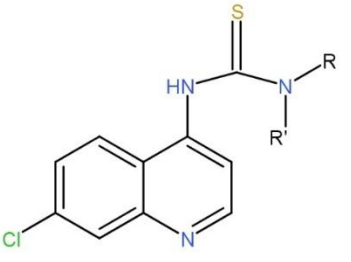


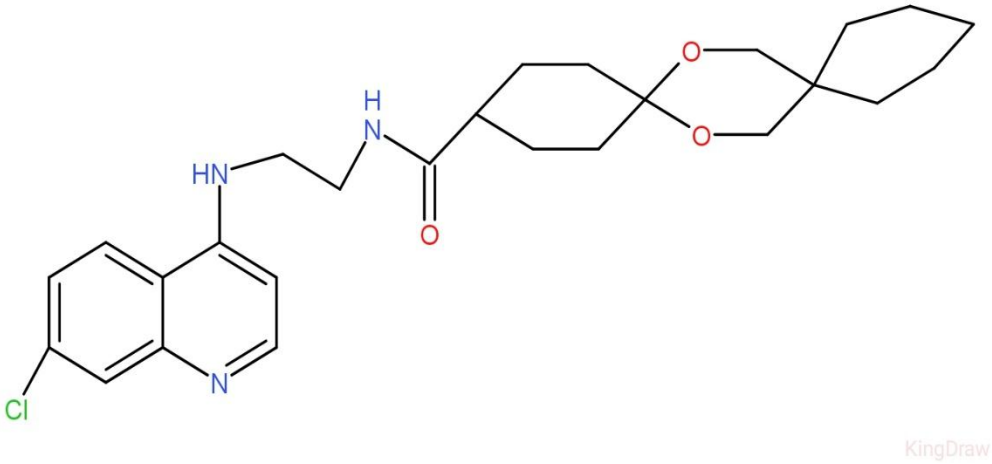




The innovating technique of combining of the two pharmacophores in a single matrix that tend to decipher a synergistic effect is also regarded as one of the new approaches for development and designing of various bioactive molecules that are potent in their nature of action.

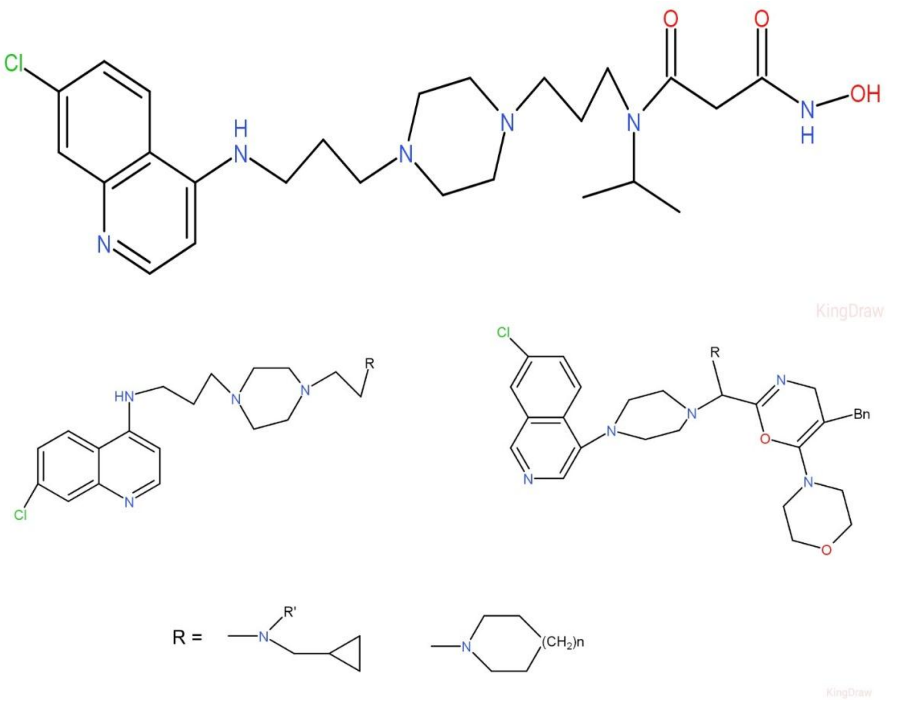






Chloroquine analogs that are incorporated with piperazine

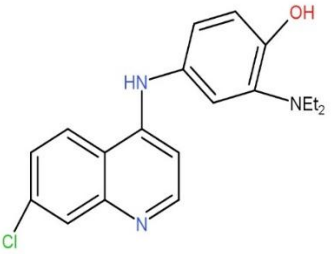
These variety of derivatives possessing the incorporation of piperazine into the analogs of chloroquine that are basically designed with approach to synthesize the various derivatives that depicts the effectiveness against various strains.



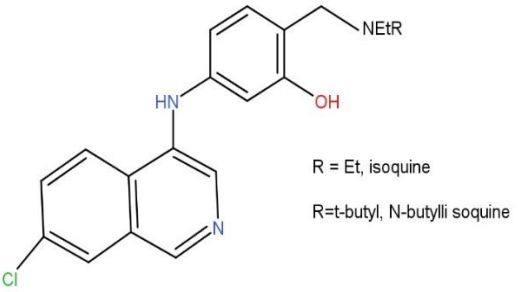
Amodiaquine analogs derivatives

Amodiaquine is basically regarded as 4-aminoquinoline that are structurally resembled to CQ that possess chain of N,N-diethyl pentane-1,4-diamine which is

illustrated to be replaced with 2-[(diethyl-amino)methyl]-phenol, which is founded to be more effective against parasitic species. Its use is signified by hepato-toxicity and tends to form agranulocytosis. Various pharmacologic research studies reveals that it cannot be oxidized to the quinone-imine that was found to be slightly-less hepato-toxic.

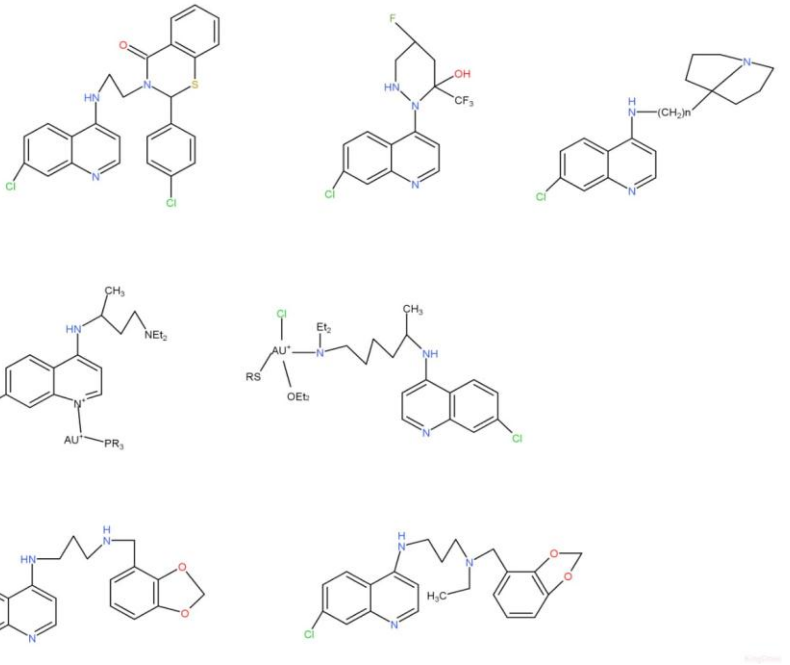


Amodiaquine



(GSK 369796)

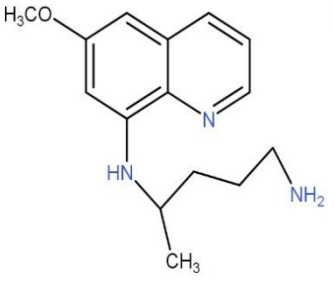
Another research scholar establish a new class of anti-malarial agents by interchanging the phenolic ring with some nuclei having aromatic that are found to resemble some of the compounds containing a nucleus of pyrrole derived analogs.



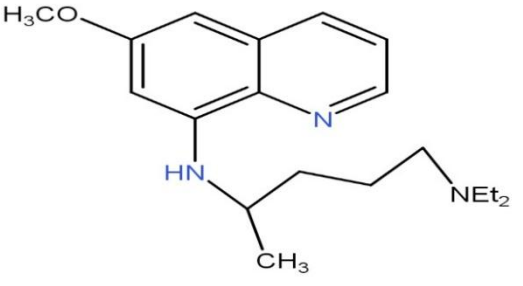
Aminoquinoline analogs derivatives

The another class of drug that have quinoline nucleus in their structure, that is often regarded as 8-amino-quinoline that is found to possess three members that plays a significant role in the treatment/mitigation of the dreadful disease of

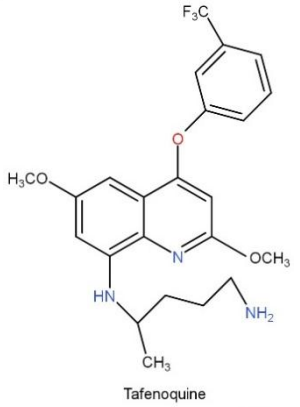
malaria, this as effectively utilized in the treatment of this ailment of malaria, these three members are arranged as primaquine, another one tafenoquine and pamaquine. These tends to play a significant role in the programme of eradication of these hazardous hypnozoites of malaria that are confined to liver cells and being employed for the prophylxais of malaria. The use of pamaquine is declined nowdays, but primaquine is found to be still playing a significant role in this eradication of malaria. Tafenoquine is still in the phase of clinical trials, so is not utilized for the purpose of prescription but it tends to possess a effective action against the plasmodium parasite and can be proved as a one of the most effective and beneficial drug in the treatment of this ailment of malaria. Chemical structures of these dervivatives i.e, the structure of primaquine, structure of pamaquine and the structure of tafenoquine are represented below. These are as represented in the following figures below:



Primaquine

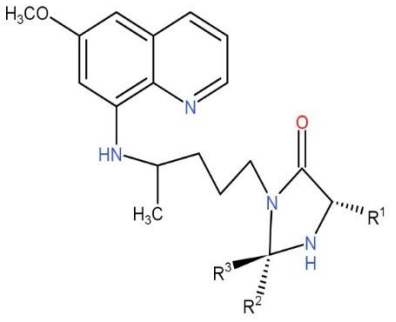


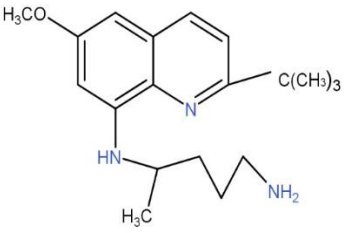
Pamaquine

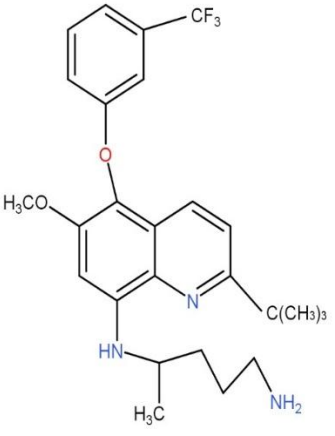


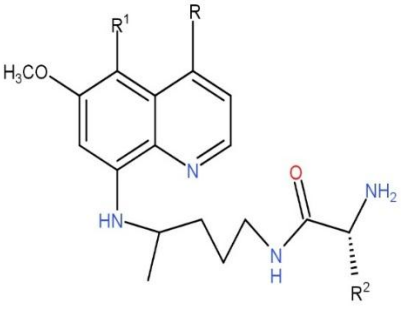
Tafenoquine

Various structure illustration of these class of drugs is still in practice and is resulting in production of more of the chemically, structurally similar compounds that are exhibiting a wide pharmacolgical activity as well as great therapeutic efficacy in the treatment of this ailment of malaria. Various reasearch and development process based on the activities of pharmacophores are tending to signify a variable response in the therapeutic potency of the drug being effective as a strong anti-malarial agent in the treatment of malarial with minimal number of adverse drug reactions, as well as side effects.



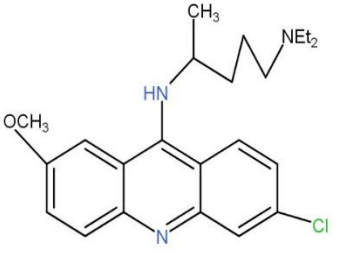




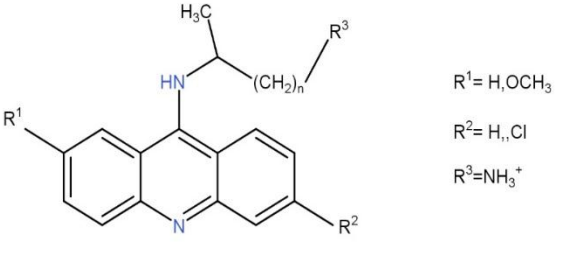


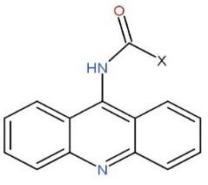
Acridine and quinoline fused analog derivatives

The derivative possessing the acridine developed quinacrine which is basically anti-protozoal in nature is also utilized as a effective antimalarial drug in the treatment of ailment of malaria. It is also utilized as a effective tool in the treatment of various protozoa induced infections that basically comprises of giardiasis, in which is a effective drug. There various modifications available in this acridine analog derivatives.

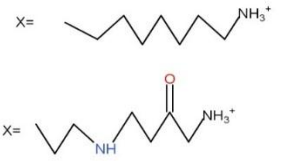


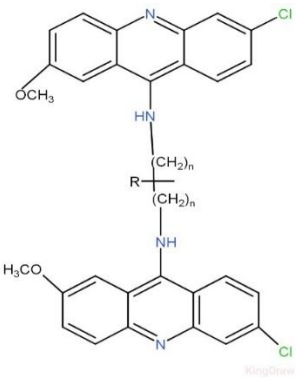
Quinacrine





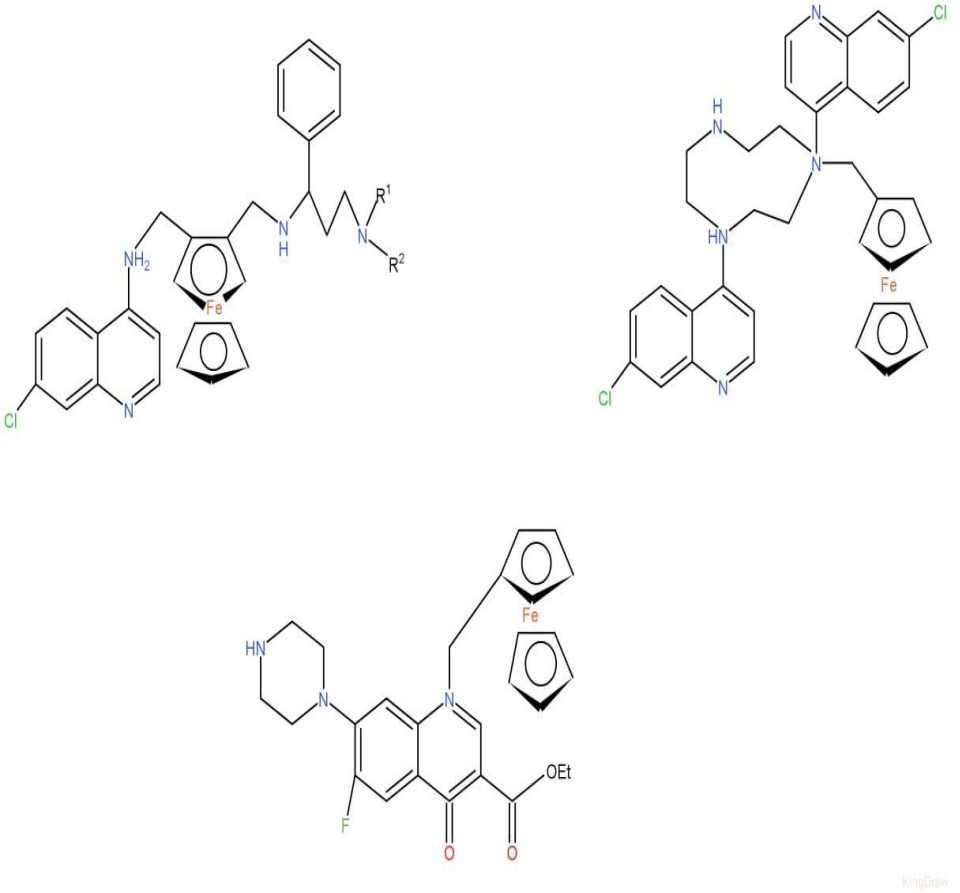
Quinacrine



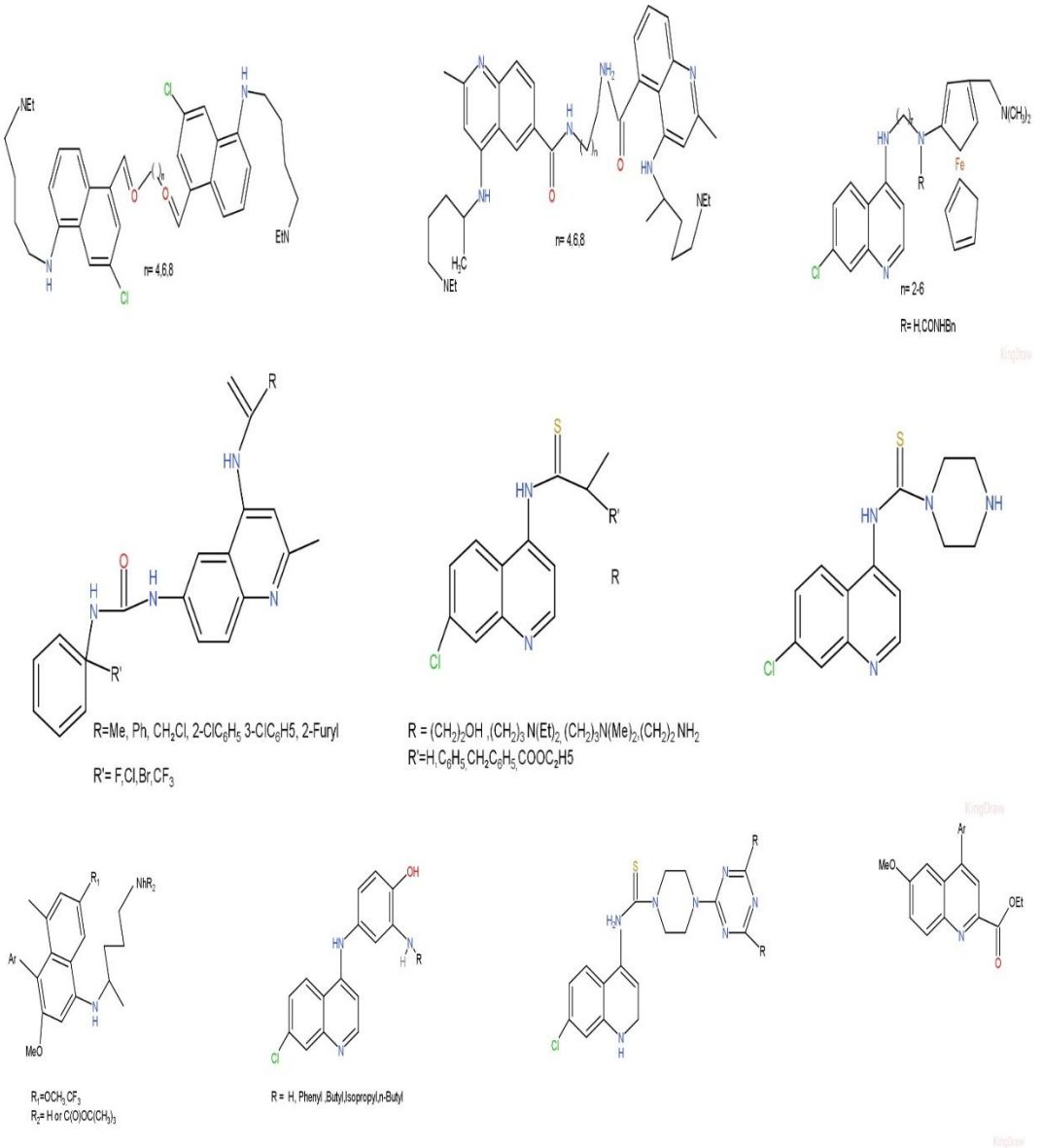


Analog Of organometallic ferrocene quinoline derivative

If we studies about the recent advances in the design and development of various newer effective potent drug-derivatives that are being employed effectively as a the chemotherapy of malaria , these tends to play a significant role. In such molecules where the presence of nucleus of ferrocene that tends to be located at various different locations within the molecules, are being tested and are calclated and their anti-malarial activity is determined. With increased potency and efficacy with respect to the treatment of this deardful ailment of malaria, which is basically a parasite of plasmodium. Following this approach of drug design and development a new series of these derived drugs which are analogs of organometallic ferrocene are effectively designed as a potent-singnificant class of drug belonging to the category of anti-malarial agents.

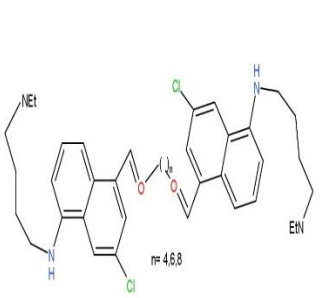


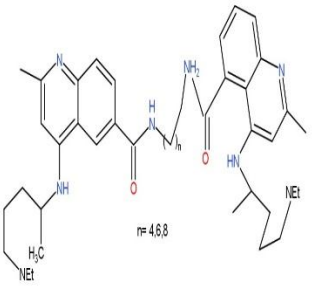
Quniolines are extensively known for their prolific antimalarial characteristics. Arious research have established various approaches for the enhancing properties. They designed a approach which illustrates that the bis-quinolines that are found to have a potent anti-malarial activity tested against the species resistant to chloroquine as well as parasites that are resistant to chloroquines. In the structure elucidaton of these compounds, it provides information that in the carbon skeleton of these derivatives is being replaced by a group resembling the properties of ferrocene.

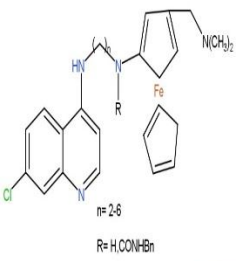


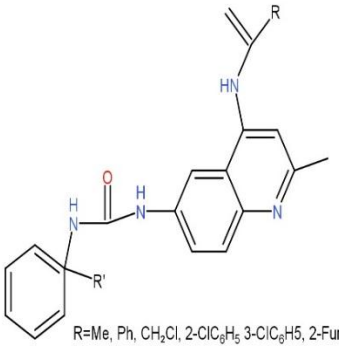
Anti-inflammatory activity of quinolines.[6]

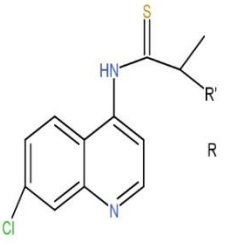
Quinolines are found to possess a greater extent of anti-inflammatory potency. This are effectively utillised for the treatment of inflammation. These were dervied in the model of arthritis depicted by a scholar scientist who worked on elaborating this activity of inflammation. And he even prooved to be successful in the setablishment of this anti-inflammatory potency of the compunds posssessing quinoline nucleus in their chemical structure.. some of structures of thses componds are demostrated below. These are as follows

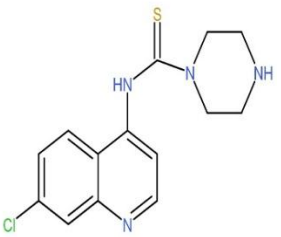


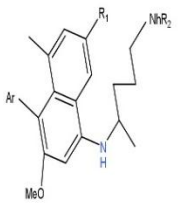


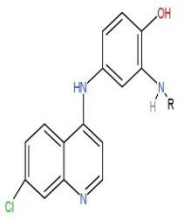


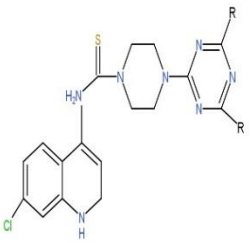


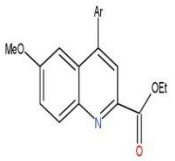






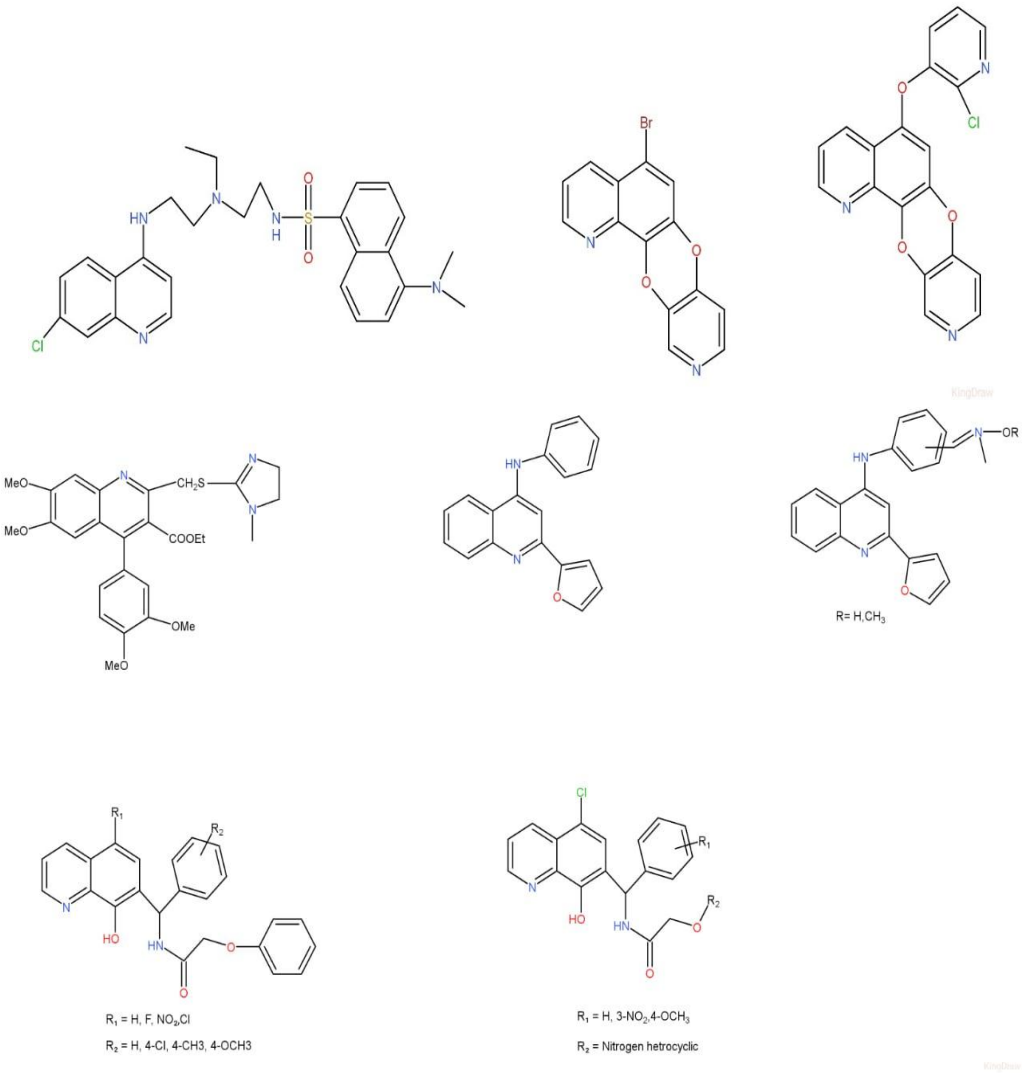






Analgesic activity of quinolines.[6]

A research scholars studies reveals that the compund 4-substituted 7 tri-fluoro-quinolines that was found to exhibit a significantly wide extent of analgesic activity. These quinoline nucleus based structural derivatives are found to possess a significant effective analgesic activity. It is found to be potent and efficacious . some of the structure of such chemical compounds possessing analgesic activity in the structure elucidated reveals of presence of quinoline nucleus. Some of the structures are given below . the chemical structure of such compounds are as follows:



References

1. Marella A, Tanwar, O.P, Saha R, Ali M.A, Srivastava S, Akhter M, Shaquiquzzaman M, Alam M.M, "Quinoline: A versatile heterocyclic", Saudi Pharmaceutical Journal,(2013):21:1-12.
2. Mondal S,"Heterocyclic Chemisry Quinoline, Isoquinoline and Indole", through https://www.researchgate.net/publication/325080072 Heeb, S, Fletcher M.P, Chhabra S.R, Diggle SP, Williams P & Camara M," Quinolones: from antibiotics to autoinducers", Published by Blackwell Publishing Ltd. All rights reserved, Rev 35 (2011) 247–274.
3. Correia S, Poeta P, Hebraud M, Capelo J.L and Igrejas G," Mechanisms of quinolone action and resistance: where do we stand?", Journal Of Medical Microbiology, 2017;66:551–559.

4. Chandrakanth B, Sastry V.G, Ramana H," Synthesis And Biological Evaluation Of Novel Quinoline Compounds", World Journal Of Pharmacy And Pharmaceutical Sciences, Volume 4, Issue 11, 1092-1101, through www.wjpps.com
5. Yamajala B.R.D. Rajesh,"Quinoline Heterocycles – Biological Activity", November 19th 2018, through https://www.intechopen.com/chapters/64434
6. echnical Report Series. Geneva: World Health Organization; 2000. WHO Expert Committee on Malaria. 20th Report.
7. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI. The global distribution of clinical episodes of Plasmodium falciparum malaria. Nature. 2005;434:214–7. [PMC free article] [PubMed]
8. Bathurst I, Hentschel C. Medicines for Malaria Venture: Sustaining antimalarial drug development. Trends Parasitology. 2006;22:301–7. [PubMed]
9. Gelb MG. Drug discovery for malaria: A very challenging and timely endeavor. Curr Opin Chem Biol. 2007;11:440–5. [PMC free article] [PubMed]
10. Rosenthal PJ. Antimalarial drug discovery: Old and new approaches. J Exp Biol. 2003;206:3735–44. [PubMed]
11. Robert A, Benoit-Vical F, Dechy-Cabaret O, Meunier B. From classical antimalarial drugs to new compounds based on the mechanism of action of artemisinin. Pure Appl Chem. 2001;73:1173–88.
12. Coslédan F, Fraisse L, Pellet A, Guillou F, Mordmüller B, Kremsner PG, et al. Selection of a trioxaquine as an antimalarial drug candidate. Proc Natl Acad Sci U S A. 2008;105:17579–84. [PMC free article] [PubMed]
13. Chen M, Theander TG, Christensen BS, Hviid L, Zhai L, Kharazmi A. Licochalcone A, a new antimalarial agent, inhibits *in vitro* growth of the human malaria parasite Plasmodium falciparum and protects mice from P.yoelii infection. Antimicrob Agents Chemothe. 1994;38:1470–5. [PMC free article] [PubMed]
14. Charris JE, Domínguez JN, Gamboa N, Rodrigues JR, Angel JE. Synthesis and antimalarial activity of E-2-quinolinylbenzocycloalcanones. Eur J Med Chem. 2005;40:875–81. [PubMed]
15. Domínguez JN, Charris JE, Lobo G, Gamboa-Domínguez N, Moreno MM, Riggione F, et al. Synthesis of quinolinyl chalcones and evaluation of their antimalarial activity. Eur J Med Chem. 2001;36:555–60.
16. Charris JE, Lobo GM, Camacho J, Ferrer R, Barazarte A, Domínguez JN, et al. Synthesis and Antimalarial Activity of (E) 2-(2'-Chloro-3'- Quinolinylmethyl idene)-5,7-Dimethoxyindanones. Lett Drug Des Discovery. 2007;4:49–54.
17. Liu M, Wilairat P, Go M-L. Antimalarial Alkoxylated and Hydroxylated Chalones: Structure—Activity Relationship Analysis. J Med Chem. 2001;44:4443–52.
18. Davis TM, Hung TY, Sim IK, Karunajeewa HA, Ilett KF. Piperaquine: A Resurgent Antimalarial Drug. Drugs. 2005;65:75–87.
19. Ayad F, Tilley L, Deady LW. Synthesis, antimalarial activity and inhibition of haem detoxification of novel bisquinolines. Bioorg Med Chem. 2001;11:2075–7.