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RECENT ADVANCES IN THE PHARMACOLOGICAL DIVERSIFICATION OF QUINOLINE DERIVATIVES

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Abstract:

Quinolines have become important compounds because of their variety of applications in medicinal, and synthetic organic chemistry as well as in the field of industrial chemistry. This review article gives information about recent reaction methods for the synthesis of quinoline derivatives. Heterocyclic compounds containing the quinoline ring play a significant role in organic synthesis and therapeutic chemistry. This article also gives information about wide biological activities like anti-cancer, anti-inflammatory, anti-bacterial, anti-malarial, anticonvulsant, antioxidant etc This review focuses on the recent progress in the synthesis of heterocyclic compounds based-quinoline and their biological activities.

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INTRODUCTION:

The heterocyclic compound is the class of cyclic organic compounds those having at least one hetero atom (i.e. atom other than carbon) in the cyclic ring system. The most common heteroatoms are nitrogen (N), oxygen (O) and sulphur (S). Heterocyclic compounds are frequently abundant in plants and animal products, and they are one of the important constituents of almost one-half of the natural organic compounds known. Alkaloids, natural dyes, drugs, proteins, enzymes etc. are some important classes of natural heterocyclic compounds. Heterocyclic compounds can be easily classified based on their electronic structure. Heterocyclic compounds are primarily classified as saturated and unsaturated. The saturated heterocyclic compounds behave like the acyclic derivatives with modified steric properties.

Quinoline 1-aza-naphthalene or benzopyridine is a nitrogen-containing heterocyclic aromatic compound. It has a molecular formula of C9H7N and its molecular weight is 129.16. The log P value is 2.04 and has an acidic pKb of 4.85 and a basic pKa of 9.5. Quinoline is a weak tertiary base. It can form a salt with acids and and displays reactions like those of pyridine and benzene. It shows both electrophilic and nucleophilic substitution reactions. It is non-toxic to humans on oral absorption and inhalation base. [1]

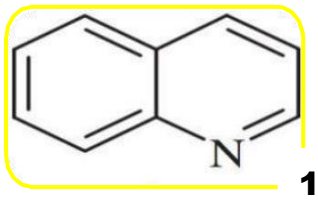


FIG 1: STRUCTURE OF QUINOLINE

Quinoline nucleus occurs in several natural compounds (2-6) (Cinchona Alkaloids) and pharmacologically active substances displaying a broad range of biological activity. Quinoline has been found to possess antimalarial, anti-bacterial, anti-cancer, antioxidant, anticonvulsant, anti-inflammatory, and anti-analgesic activity. Examples are Chloroquine, Ciprofloxacin, Clioquinol, Quercetin, Quinidine,T-5224.

DERIVATIVES OF QUINOLINE: -

Several established protocols are there for the synthesis of quinoline rings, which can be well modified to prepare several differently substituted quinolines.

Drugs containing quinoline in their structure: -

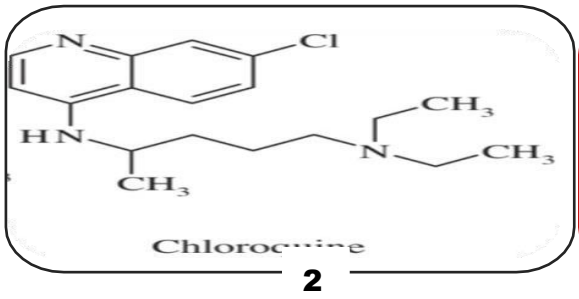


FIG 2:STRUCTURE OF CHLOROQUINE

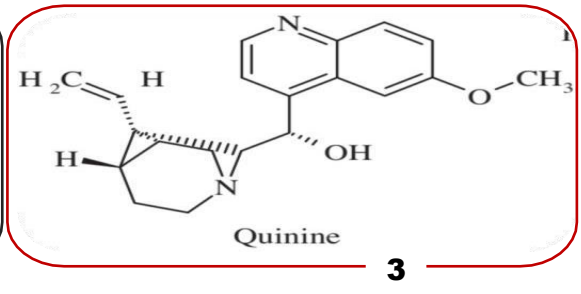


FIG 3:STRUCTURE OF QUININE

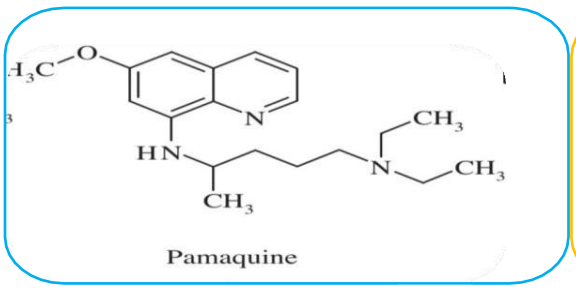


FIG 4:STRUCTURE OF PAMAQU 4

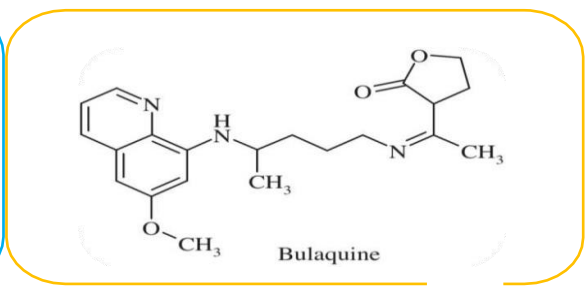


FIG 5:STRUCTURE OF BULAQ

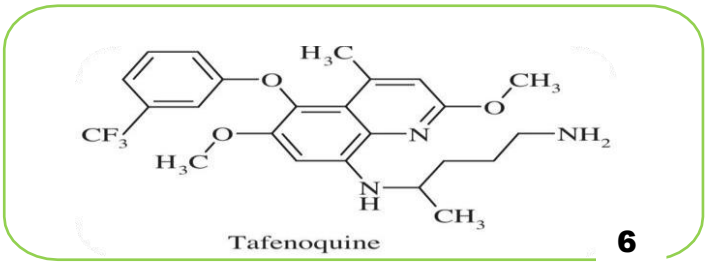


FIG 6:STRUCTURE OF TAFENOQUINE

PREPARATION METHOD OF QUINOLINE: -

1 . Skraup synthesis method:

This method is the most widely used method for the preparation of quinoline. In this method, A primary aromatic amine and glycerol are heated at a high temperature in the presence of sulphuric acid and mild oxidizing agents like nitrobenzene or the presence of peroxides like arsenic peroxide. Ferrous sulphate { Feso4 } or boric acid { H3Bo3 } is generally added to make the reaction less violent because scrap synthesis is a highly exothermic reaction.[2]

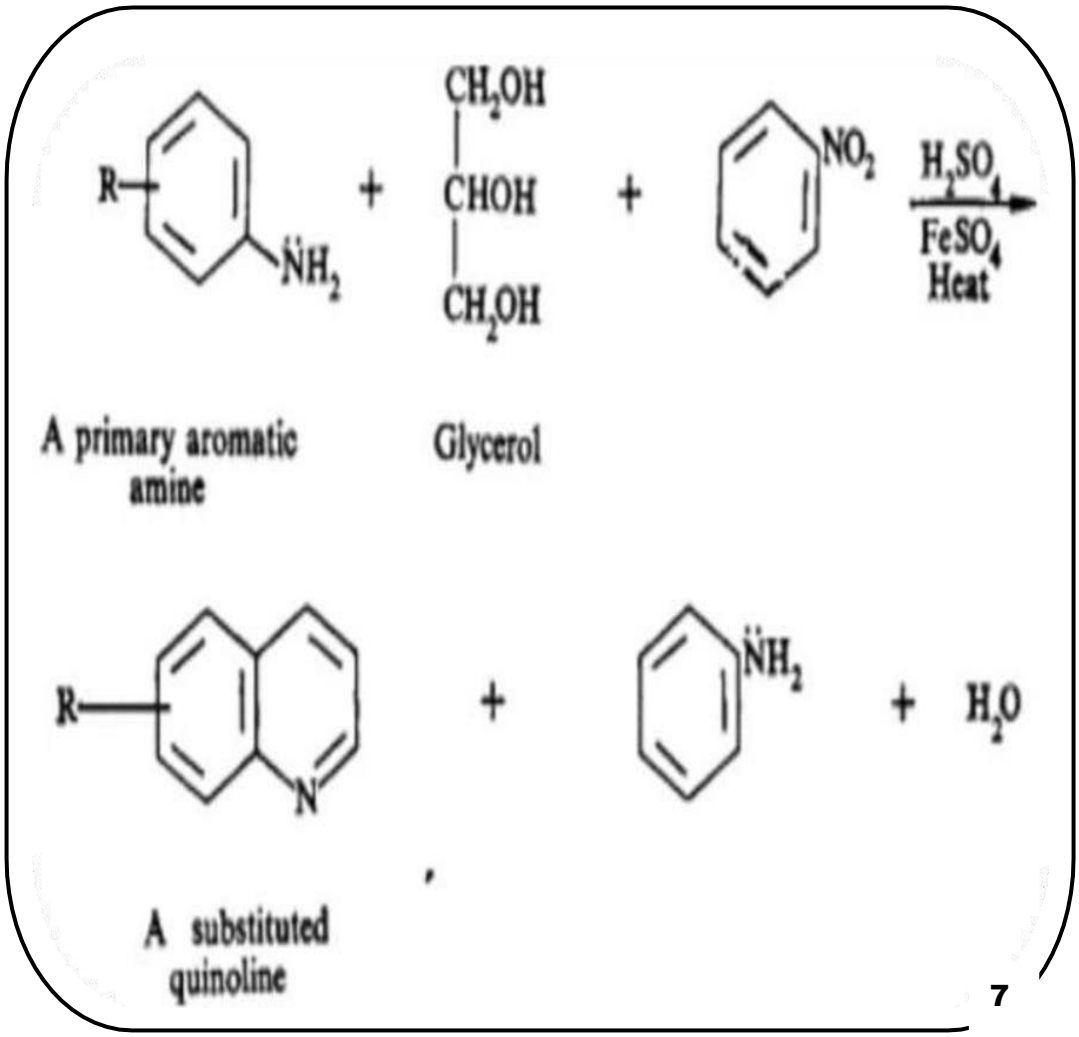


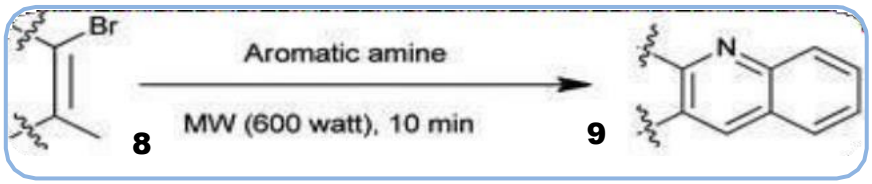
FIG 7: SKRAUP SYNTHESIS

RECENT METHODS OF PREPARATIONS OF QUINOLINE:
VARIOUS REACTION SCHEMES: -

SCHEME 1

The catalyst could be easily recovered by simple filtration and could be reused for several cycles without any significant loss of its catalytic activity. Moreover, no metal was detected in the final product which confirms the green nature of the present method. This makes the method useful and attractive for the synthesis of quinoline derivatives. [3]

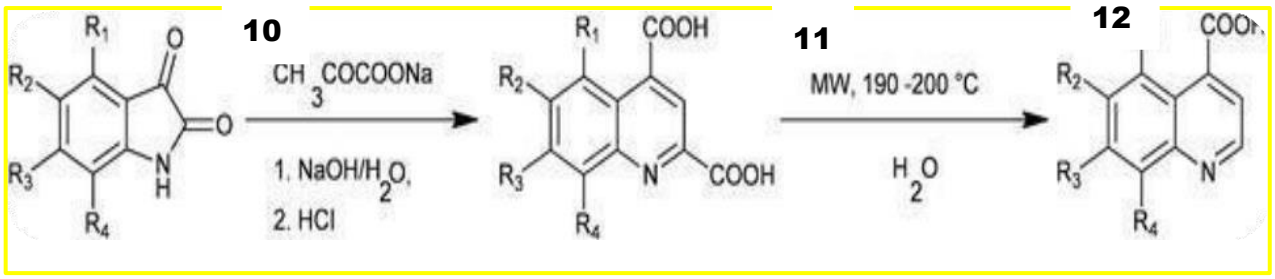
A synthesis of steroidal and non-steroidal quinoline derivatives has been established by Gogoi *et al.*. In this method, steroidal quinoline derivatives were synthesized from a one-pot reaction of steroidal β-bromovinyl aldehydes and arylamines in high yield using microwave irradiation without the use of a catalyst and in a solvent-free condition. This methodology offers an environment-friendly 'green' alternative organic synthesis.



SCHEME 1- SYNTHESIS OF QUINOLINE DERIVATIVE

SCHEME 2

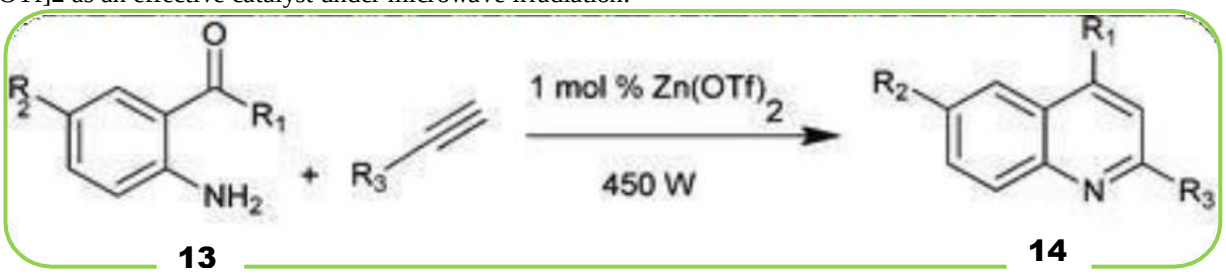
Facile microwave-assisted processes suitable for the preparation of a series of quinoline-4-carboxylic acids have been introduced by Zhu and co-workers. In this Pfitzinger type of reaction, a condensation reaction between isatins and sodium pyruvate to give quinoline-2,4- dicarboxylic acid (QDC) is carried out under microwave conditions which optimise reaction solvent, time and temperature. The subsequent decarboxylation reaction of QDCs in water instead of toxic nitrobenzene under MW was also promoted successfully.[4]



SCHEME 2- SYNTHESIS OF QUINOLINE DERIVATIVE

SCHEME 3

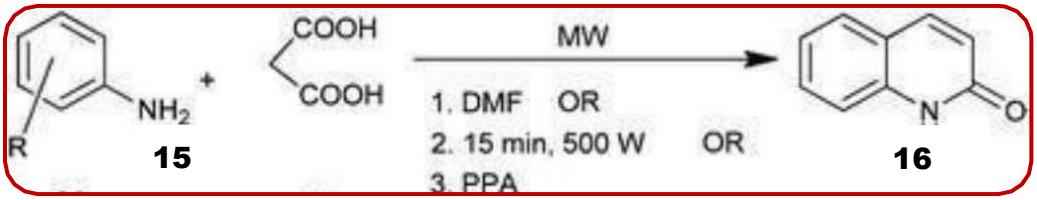
Quinoline derivatives were synthesized by employing amino acetophenone and phenylacetylene in the presence of ZN[OTf]2 as an effective catalyst under microwave irradiation. [5]



SCHEME 3- SYNTHESIS OF QUINOLINE DERIVATIVE

SCHEME 4

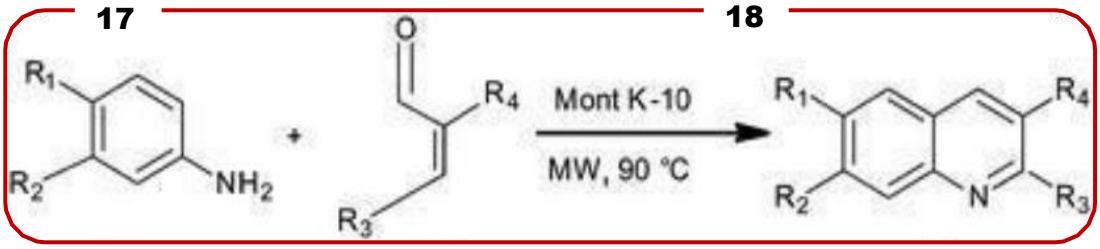
3-Unsubstituted 4-hydroxyquinoline-2(1*H*)-one was synthesized using substituted aromatic amine and malonic acid under microwave irradiation in dimethyl formamide, without employing any solvent and using polyphosphoric acid (PPA). Operational simplicity and high yield in a significantly very short reaction time make this procedure a useful and attractive alternative to the currently available methods.[6]



SCHEME 4- SYNTHESIS OF QUINOLINE DERIVATIVE

SCHEME 5

Montmorillonite K10 clay-catalyzed synthesis of quinoline derivative has been disclosed by Nagendrappa *et al.* by employing aniline derivatives and cinnamaldehyde. The mechanism follows a domino process involving cyclization followed by dehydration and then after oxidation delivers quinolines. The reaction was carried out under solvent-free conditions and with the assistance of microwave irradiation.[7]



SCHEME 5- SYNTHESIS OF QUINOLINE DERIVATIVE

RECENT ADVANCES IN THE PHARMACOLOGICAL ACTIVITIES OF QUINOLINE DERIVATIVES:
ANTI-BACTERIAL ACTIVITY OF QUINOLINE DERIVATIVES:

Quinoline compounds have been studied for their anti-bacterial properties. Some research suggests they can inhibit bacterial growth by targeting essential cellular processes. However, the specific mechanism can vary depending on the structure of the quinoline derivative and the bacterial strain being targeted.

Quinoline derivatives have shown promising antibacterial activity against a variety of pathogens, For example, quinoline antibiotics like Ciprofloxacin and levoflaxacin are widely used to treat bacterial infections, Additionally, researchers continue to explore new quinoline derivatives for their antibacterial potential. [8]

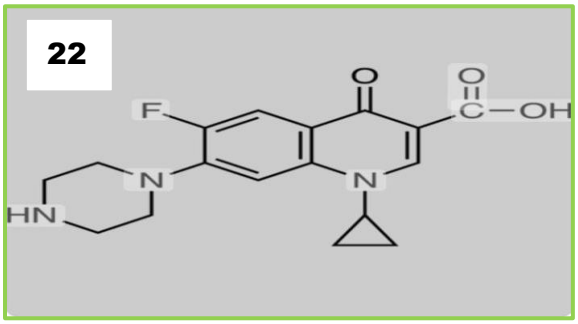


Fig 15 : ANTI-BACTERIAL ACTIVITY OF QUINOLINE DERIVATIVE

ANTI-MALARIAL ACTIVITY OF QUINOLINE DERIVATIVES: -

Quinoline, a heterocyclic compound, exhibits potent anti-malarial activity due to its ability to interfere with the life cycle of the malaria parasite. Quinine, a natural quinoline derivative from the cinchona tree, has been used for centuries to treat malaria. Modern anti-malarial drugs like chloroquine and mefloquine are synthetic synthetic quinoline derivatives that have proven highly effective against plasmodium species. The development of quinoline-based antimalarials, including artemisinin combination therapies(ACTs), has significantly improved the management and control of malaria, a disease that continues to pose a global health threat.[9]

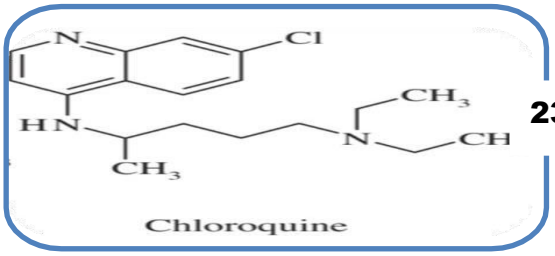


FIG 16: ANTI-MALARIAL ACTIVITY OF QUINOLINE DERIVATIVE

MECHANISM OF ACTION OF CHLOROQUINE: -

Chloroquine primarily works by interfering with the parasite's ability to digest haemoglobin within the red blood cells,disrupting its metabolic processes and ultimately leading to it's death. Additionally, it may also interfere with the parasite's ability to access and utilize certain nutrients essential for its survival.

ANTI-CANCER ACTIVITIES OF QUINOLINE DERIVATIVES:-

Quinoline compounds have demonstrated significant anti-cancer activity, offering promise in the fight against this devastating disease. One notable example is hydroxyquinoline, which exhibits potent anti-cancer properties. Studies have shown that hydroxyquinoline can inhibit the growth of cancer cells by disrupting critical cellular processes and including apoptosis, or programmed cell death. The ability of This compound to interfere with DNA replication and inhibit angiogenesis, the formation of new blood vessels to supply tumours, makes it a valuable candidate in cancer therapy.

One example of a quinoline derivative with anti-cancer activity is Camptothecin. Camptothecin and its derivatives, such as itinotecan and topotecan, are used in cancer chemotherapy. They inhibit the enzyme topoisomerase 1, which is involved in DNA replication and transcription. By inhibiting this enzyme, camptothecin derivatives cause DNA damage and ultimately induce cancer cell death. They are used to treat various types of cancers, including colorectal, ovarian, and lung cancers.[10]

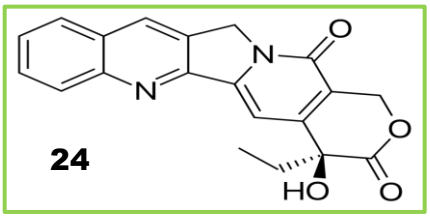


FIG 17:ANTI-CANCER ACTIVITY OF QUINOLINE DERIVATIVE

ANTIOXIDANT ACTIVITY:-

Quinoline compounds have been studied for their antioxidant properties due to their ability to scavenge free radicals and inhibit oxidative stress. Research suggests that quinoline derivatives exhibit antioxidant activity through various mechanisms, including metal chelation, radical scavenging, and inhibition of lipid peroxidation. However, the specific antioxidant activity of a quinoline compound can vary depending on its chemical structure and functional groups.

One example of a quinoline derivative with antioxidant activity is 2- Phenylquinoline (PQ). PQ has been studied for its ability to scavenge free radicles and reduce oxidative stress-induced damage in cells and tissues. It acts by donating hydrogen atoms or electrons to stabilise free radicles, thereby preventing them from causing cellular damage. PQ's antioxidant properties make it a potential candidate for the development of therapies targetting oxidative stress-related diseases, such as neurodegenerative disorders and cardiovascular diseases. [11]

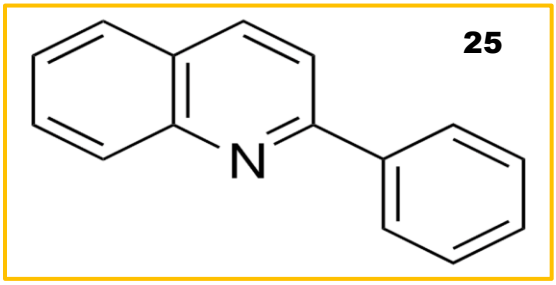


Fig18: ANTI-OXIDANT ACTIVITY OF QUINOLINE DERIVATIVE

ANTICONVULSANT ACTIVITY :-

Quinoline derivatives have shown promising anti-convulsant activity in preclinical studies studies. They exhibit their effects by modulating the neurotransmitter system and ion channels involved in seizure generation and propagation. Several quinoline compounds have demonstrated efficacy in animal models of epilepsy, making them potential candidates for further development as anti-convulsant drugs.

Quinoline derivatives have shown promise in exhibiting anti-convulsant activity. For example, quinidine, a quinoline alkaloid, has been studied for its potential in managing seizures and epilepsy. Additionally, quinine, another quinine alkaloi **26** been investigated for its anti-convulsant prop although its primary use is as an antimalarial medication. These compounds have demonstrated effects on various neurotransmitter systems, including modulation of voltage-gated ion channels, which are implicated in the control of neuronal excitability and seizure generation. [12]

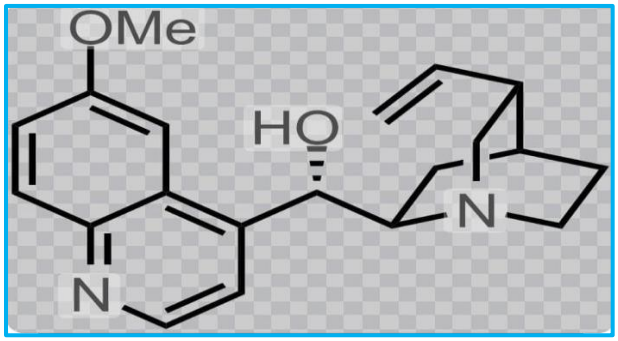


Fig 19: ANTICONVULSANT ACTIVITY OF QUINOLINE DERIVATIVE

ANTI-INFLAMMATORY ACTIVITY:

Quinoline derivatives have been studied for their anti-inflammatory properties. It inhibit inflammation by modulating various pathways, such as inhibiting the production of inflammatory cytokinins or interfering with enzymes evolved in the inflammatory process. However, the specific mechanisms and efficacy may vary depending on the specific quinoline derivative.

EX: A recent example of a quinoline compound with anti-inflammatory activity is T-5224(3-{propionic acid) 5-[4-(cyclopentyloxy)-2-hydroxybenzotl]-2-[(3-hydroxy-1,2-benzisoxazol-6 yl)methoxy]phenyl}.This compound has been studied for its potential therapeutic effects in inflammatory diseases like rheumatoid arthritis and inflammatory bowel disease. T-5224 inhibits the activity of a protein called called AP-1, which plays a role in regulating the expression of genes involved in inflammatory. [13]

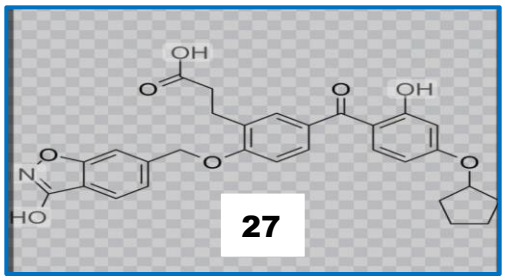


FIG 20: ANTI-INFLAMMATORY ACTIVITY OF QUINOLINE DERIVATIVE

ANTI-HIV ACTIVITY:-

Quinoline derivatives have been investigated as potential anti-HIV agents, particularly in the context of drug discovery and development. Some quinoline derivatives have shown promising results in preclinical studies by targetting various stages of the HIV life cycle or interfering with viral replication. However, furthur research is needed to asses their efficacy and safety foe clinical use.

One example for the anti-HIV activity is TMC-120(dapavirine), which is a non-nucleoside reverse transcriptase inhibitor(NNRTI). Dapavirine binds to and inhibits the HIV-1 reverse transcriptase enzyme, thereby preventing the conversion of viral RNA into DNA, an essential step in the HIV replication cycle. Dapivirine has been eveloped as a microbicide for topical use to prevent HIV transmission, particularly in women. It's been studied in various clinical trials and has shown promise as a potential tool for HIV prevention. [14]

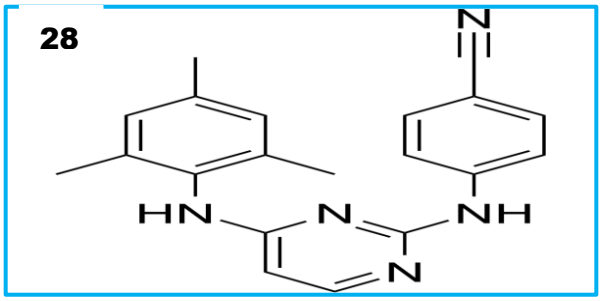


FIG 21 :ANTI-HIV ACTIVITY OF QUINOLINE DERIVATIVE

ANTI-FUNGAL ACTIVITY:-

Quinoline derivatives have been investigated for their potential anti-fungal activity. One example is Clioquinol, which has been used as a topical anti-fugal agent in the treatment of skin infections caused by fungi such as Candida and Tricophyton species.

Clioquinol functions by disrupting essential cellular processes in fungi, such as interfering with DNA synthesis and inhibiting metal-dependent enzymes crucial for fungal growth and survival. While it has been mostly replaced by newer antifungal activity of some quinoline derivatives. [15]

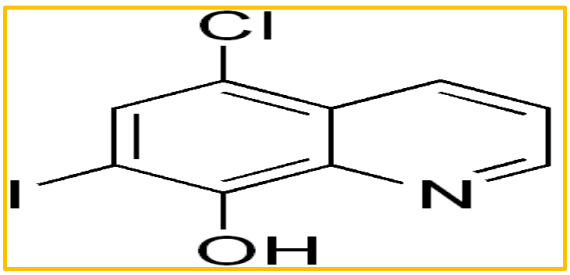


FIG 23: ANTI-FUNGAL ACTIVITY OF QUINOLINE DERIVATIVE

URINARY TRACT INFECTIONS OF QUINOLINE:-

Quinoline derivatives are commonly used in the treatment of urinary tract infections(UTI's). Examples of quinoline antibiotics include ciprofloxacin, levoflaxacin, and norflaxacin.

These antibiotics work by inhibiting the bacterial DNA gyrase or topoisomerase IV enzymes, which are essential for bacterial DNA replication and repair. By interfering with these enzymes, quinoline antibiotics prevent the bacteria from multiplying and ultimately lead to their death.[16]

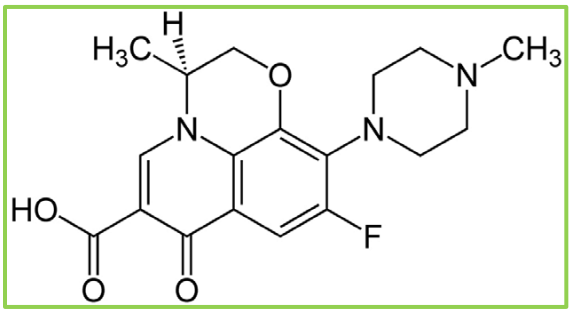


FIG 24: URINARY TRACT INFECTIONS OF QUINOLINE DERIVATIVE

CONCLUSION:

In summary, I conclude that this comprehensive review of quinoline and its biological activities has unveiled the versatile nature of quinoline compounds. these molecules exhibit a wide range of biological activities, including anti-malarial, anti-bacterial, anti-cancer, anti-inflammatory, anti-convulsant, and anti-oxidant activities. the importance of quinoline derivatives in drug development and therapeutic interventions. it holds promise for the development of novel treatments and medicines, benefiting both scientific advancements and human health. Because of various pharmacological activities quinoline became important pharmacophore in the design of drug molecules.

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