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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF QUINOLINES

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Abstract:

Quinoline, a N-based aromatic compound has numerous applications in various industries, including pharmaceuticals, agrochemicals, dyestuffs, and materials. It has antiprotozoal, antitubercular, anticancer, antipsychotics, anti-inflammatory, antioxidant, anti-HIV, antifungal, efflux pump inhibitors, neurodegenerative diseases and lupus treatment. Quinine and quinidine alkaloids from Cinchona bark contain quinoline scaffolds, making it a key component in clinically used drugs. Various methods have been developed to synthesize quinoline derivatives, including the Gould-Jacob quinoline synthesis, Friedlander quinoline synthesis, Pfitzinger quinoline synthesis, Skraup/Doebner-von Miller quinoline synthesis, and Combes/Conrad-Limpach synthesis.

Keywords; *Agrochemicals, Cinchona, cyclodehydration, hypotensive effects, rheumatoid arthiritis*

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INTRODUCTION:

Quinoline, a significant N-based heterocyclic aromatic compound, is widely researched due to its diverse applications. Its main sources include petroleum, coal processing, wood preservation, and shale oil. Quinoline derivatives are found in natural products, including alkaloids. First extracted from coal tar in 1834, it remains the primary commercial Source**.(1)** Quinoline, a weak tertiary base extracted from coal tar in 1834, is a key structural componentin various pharmaceuticals, agrochemicals, dyestuffs, and materials. It has diverse pharmacological activities, including antiprotozoal, antitubercular, anticancer, antipsychotics, anti-inflammatory, antioxidant, anti-HIV, antifungal, efflux pump inhibitors, neurodegenerative diseases, and lupus treatment. Quinine and quinidine alkaloids from Cinchona bark also contain quinoline scaffold. Quinoline is a key component in several clinically used drugs, particularly antimalarial drugs. Camptothecin analogues, such as topotecan and irinotecan, have been approved for cancer chemotherapy, while another analog, exatecan, is under clinical study. Mappicine ketone, a fused quinoline natural product, has antiviral properties against herpes viruses and HCMV**. (2)** Its structural isomers, isocrytolepine, and neocryptolepine, also possess antimalarial activity. Quinoline has also been used in other diseases, such as fluoroquinolone antibiotics, pitavastatin, lenvatinib, and its structural analogs. CHM-1-P-Na is a preclinical anticancer agent with excellent antitumor activity in a SKOV-3 xenograft nude**. (3)** The twelve principles of "Green Chemistry" were established in the 1990s to meet the needs of the present generation without compromising future generations. Industries and academia are now striving to comply with these principles. Classical synthetic routes for synthesizing quinolines, such as Combes, Skraup, Conrad-Limpach, Povarov, Doebner, Doebner-Miller, Gould-Jacobs, and Riehm, are effective but not environmentally friendly due to waste production, operational complexity, high temperatures, and long reaction periods. To address these concerns, new greener methods are needed to increase yield, selectivity, productivity, and environmental sustainability**. (4)**

Synthesis of quinoline and its derivatives:

Quinoline and its derivatives have been a subject of interest for both synthetic and biological chemists due to their diverse chemical and pharmacological properties. Various methods have been developed to synthesize quinoline derivatives, including those using metallic or organometellic reagents. The quinoline ring system is found in various natural products, particularly alkaloids, and is often used for designing synthetic compounds with different pharmacological properties. Natural products of the quinoline skeleton are used in medicine and as lead molecules for developing newer and potent molecules. Quinine, an active ingredient from Cinchona trees, has been used for malaria treatment and has been used in the development of new antimalarial drugs. **(5)** Scholars have explored various synthesis protocols for constructing and functionalizing quinoline scaffolds, including classical methods like Gould-Jacob, Friedland, Pfitzzinger, Skraup, Doebner-von Miller, Conrad-Limpach, transition metal catalysed, ultrasound, and greener chemical processes. **(6)**

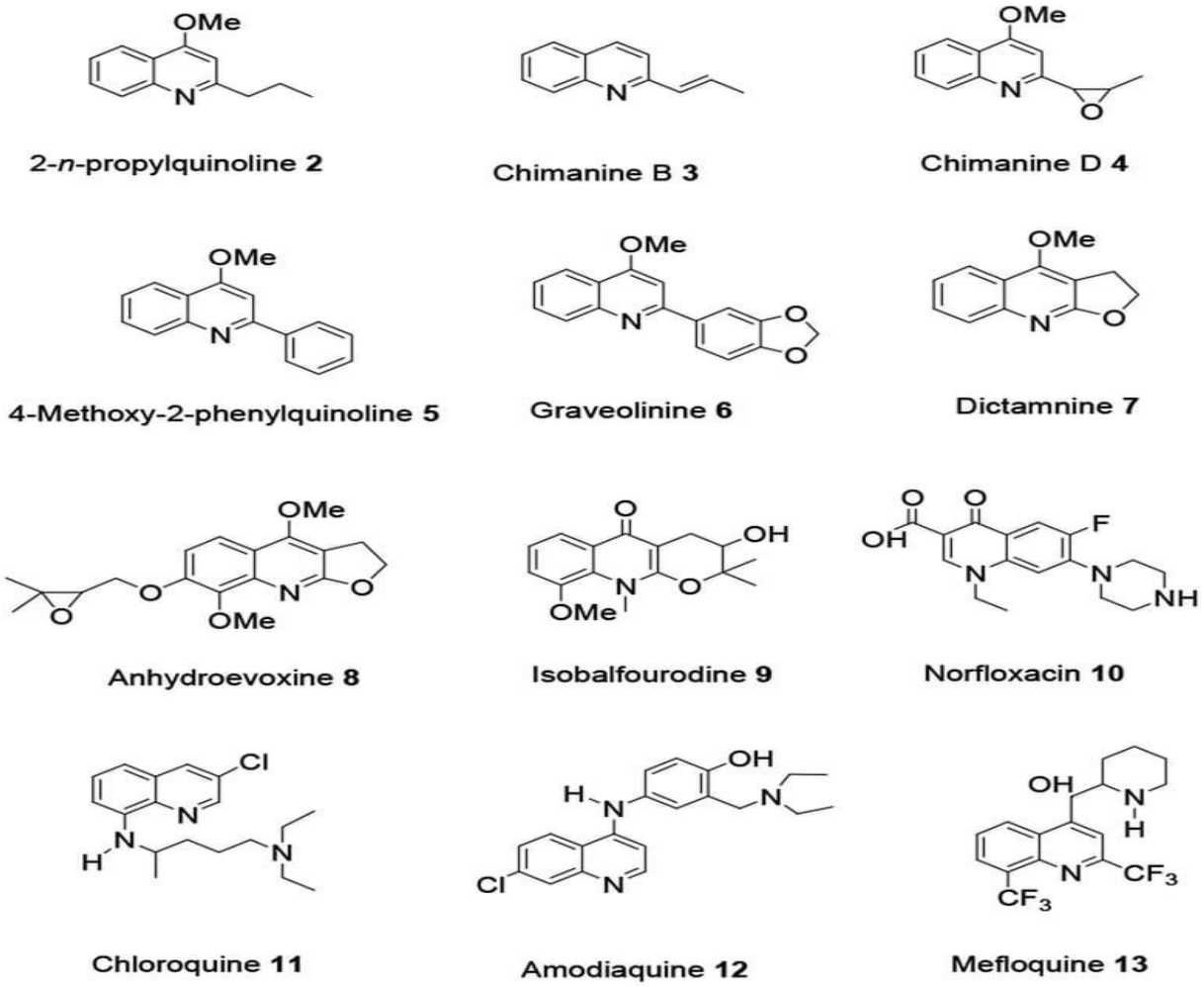

Fig: 1 Structures of bioactive compounds from natural sources

Gould–Jacob quinoline synthesis:

Organoselenium compounds are interesting for their potential applications in electronics and biological activity. They can be found in anti-inflammatory agents, immunomodifiers, cytokine inducers, enzyme inhibitors, virucides, or bactericides. Selenadiazoloquinolones, such as Ebselen, are practically nontoxic and have antitumor activity. However, inorganic selenium compounds represent higher danger due to their higher volatility. To prepare 7-substituted selenadiazoloquinolones 9 and 10, a condensed heterocyclic system was created, which were tested for antimicrobial activity on four strains of bacteria, yeasts, and filamentous fungi. **(7)** UVA photoexcitation of selenadiazoloquinolones in dimethylsulfoxide or acetonitrile resulted in the formation of paramagnetic species coupled with molecular oxygen activation generating a superoxide radical anion or singlet oxygen, asevidenced by EPR spectroscopy. The most efficient and convenient route towards quinolones involves the Goulde Jacobs ścorresponding nitro derivative. The key intermediate for the synthesis of selenadiazoloquinolones 9 is 4-aminobenzoselenadiazole 4. However, attempts to prepare amine 4 using various reducing agents, such as NaBH4, catalytic hydrogenation on Raney nickel, or palladium on charcoal failed. Another approach to amine 4 involved the cyclization of 1,2,3-triaminobenzene (3) with aqueous selenium dioxide solution. However, the use of not so readily available 2,6-dinitritroaniline (1) led to unsatisfactorily low yields. To avoid these drawbacks, 4-nitrobenzothiadiazole 6, readily accessible in large quantities by nitration of benzothiadiazole, was used as a starting material for the preparation of the key amine 4. Nucleophilic vinylic substitutions proceeded smoothly with good yields in refluxing methanol or ethanol. The cyclization reaction prepares 4-hydroxyquinoline 16, a key component in the preparation of commercially available drugs like octafenine and glafenine, using aniline and diethyl ethoxymethylmalonate. **(8)**

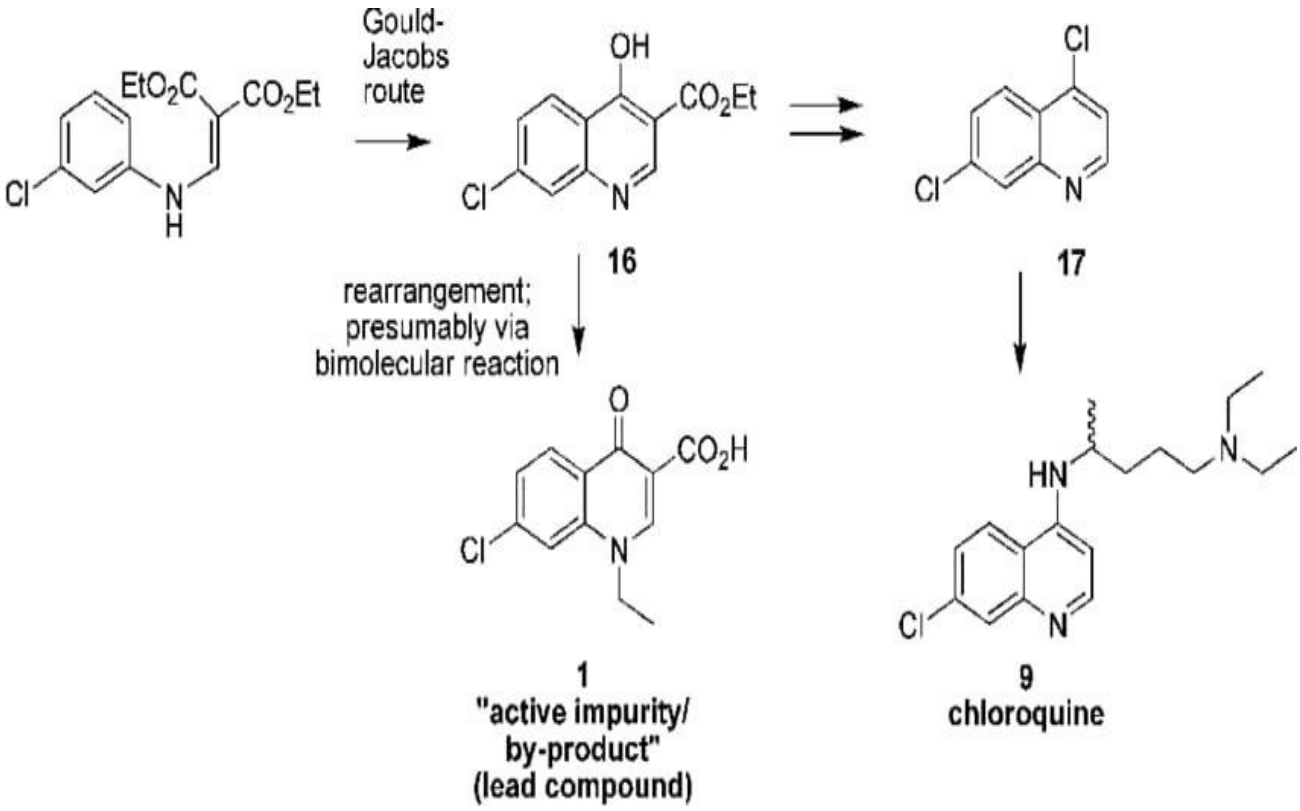

Fig:2 Gould–Jacob quinoline synthesis

Friedlander quinoline synthesis:

In this procedure ortho-substitution of aniline 17 and aldehyde or ketone 18 with a reactive a-methylene group via condensation followed by cyclodehydration reactions affords compound 19 . In this reaction procedure, regioselectivity is a challenging issue when unsymmetrical ketones are used.5 The reaction is well catalysed using a base or acid, such as a Brønsted acid or a Lewis acid, and ionic liquids can also activate the reaction well. Furthermore, it can proceed smoothly without a catalyst by heating the mixture. The merit of this reaction procedure is the scope of substrates of various functional groups that are well tolerated on both arylamine and ketone moieties**. (9)**

The authors developed a three-component reaction protocol using 2-bromobenzaldehyde, acyclic or cyclic 1,3-diketone, and sodium azide to prepare quinoline 22 in good yields. The process involves copper salt-D-glucose reduction in aqueous ethanol, proline as a ligand and proton source, and an Ullmanntype coupling reaction. The method works well with electron-donating and electron-withdrawing substituent groups. The authors also used a one-step and one-pot method to synthesize quinoline-4-carboxylic acids in water. **(10)**

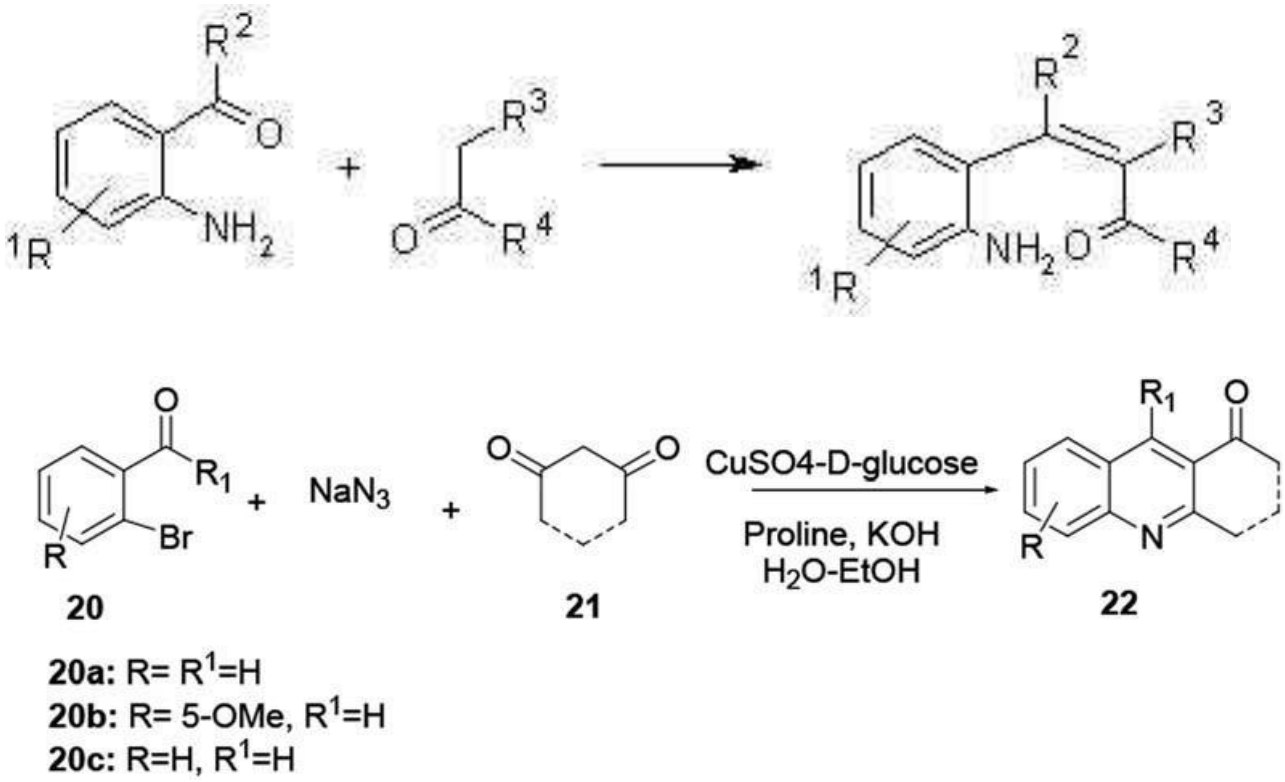

FIG:3 General reaction scheme of modified Friedla¨nder quinoline synthesis.

Pfitzinger quinoline synthesis:

The Pńtzinger quinoline synthesis is a method that involves isatin reacting with a-methylene carbonyl compound in ethanol to produce a substituted quinoline derivative. This procedure is an extension of the Friedl¨ander quinoline synthesis protocol and relies on more stable isatin varieties. Elghamry and coworkers used a similar one-step and one-pot method to synthesize quinoline-4-carboxylic acids in water, using enaminone as a replacement for 1,3-dicarbinols. **(11)**

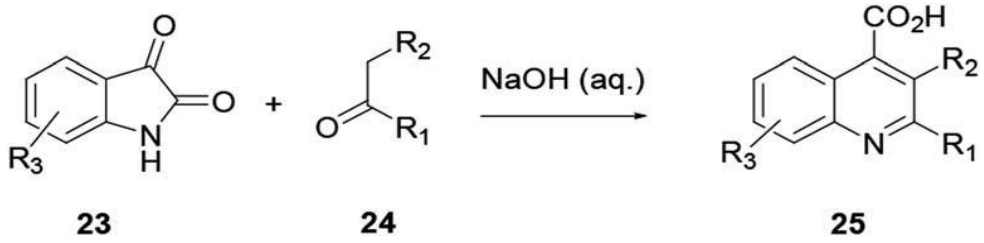

Fig 4: General reaction scheme of the Pfitzinger quinoline synthesis.

Skraup/Doebner–von Miller quinoline synthesis:

Skraup and co-workers discovered a quinoline synthesis using aniline and glycerine in a strong acid and oxidant reaction. The Doebner-von Miller protocol, which involves substituting acrolein with aniline, is a rapid and green method for quinoline synthesis. However, both methods are violently exothermic and require a variety of oxidants and an acidic medium. Yalgin and co-workers report a modified Doebner-von Miller reaction protocol for 2-methylquinoline synthesis, offering a more efficient and environmentally friendly method. **(12)**

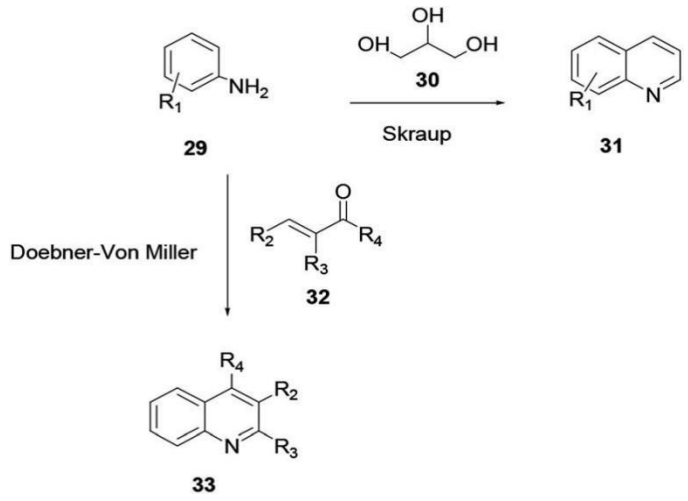

Fig 5: General reaction scheme of Skraup/Doebner-von miller quinoline synthesis

Combes/Conrad–Limpach quinoline synthesis:
The Combes/Conrad-Limpach reaction involves condensation of a primary aryl amine witha 1,3-diketone or b-keto-aldehyde, resulting in an enamine intermediate heated in strong acid and cyclodehydrated to afford quinoline. This process can be used to prepare various quinoline derivatives using b-ketoester. **(13)**

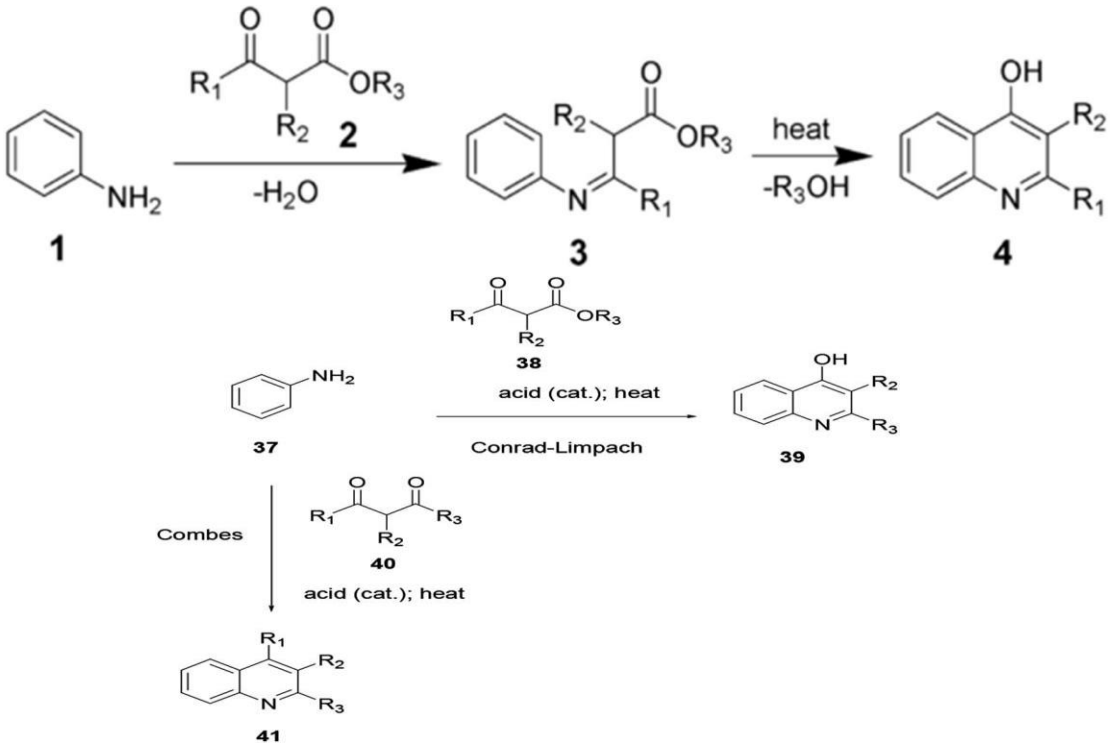

Fig 6: General reaction scheme of the Combes/Conrad–Lim pach quinoline synthesis.

BIOLOGICAL ACTIVITY OF QUINOLINES:
They have been demonstrated to have high biological potential due to their anticancer, antimycobacterial, antimicrobial, anticonvulsant, anti-inflammatory, cardiovascular, antibacterial, antifungal, and antiviral activities

Anti-cancer activity:
Cancer is the second leading cause of death in humans, with 13.3% of global deaths in 2008 being due to cancer. Common cancers include lung, stomach, liver, colon, and breast cancer. The global number of cancer deaths is expected to rise to 9 million by 2015 and 11.4 million by 2030. The search for new anticancer agents is a challenging task. Quinoline derivatives fused with heterocycles have shown potent anticancer activity, targeting sites like topoisomerase I, telomerase, farnasyl transferase, Src tyrosine kinase, and protein kinase CK-

II. New derivatives of 2-phenyl quinoline have strong binding to DNA and inhibit nucleotide exchange processes on oncogenic Ras genes. The study tested the antitumor activities of synthesized compounds against liver carcinoma cell lines (HEPG2) and human breast cancer cell lines (MCF-7). The most promising compounds showed 60% cytotoxicity or more at a concentration of 100 mg ml-1. Cell culture cytotoxicity assays were carried out as previouslydescribed. Results showed that compounds 16 and 19 exhibited moderate activity against the HEPG2 cell line compared to the reference drug doxorubicin. Compound 4 was the most potent compound tested, while compounds 19 and 8 exhibited moderate activity. Compounds 17, 12,and 7 exhibited a weak cytotoxic effect in both cell lines. The synthesized compounds were supplied to the Bioassay-Cell Culture Laboratory for in vitro primary antitumor screening on hepato-cellular carcinoma (HEPG2) and Caucasian breast adenocarcinoma (MCF7). Cell viability was assessed by the mitochondrial-dependent reduction of yellow MTT to purple formazan. The IC50 values were calculated using the respective regression equation. The results showed that some of the tested compounds showed significant acts against HEPG2 andMCF-7 cell lines. **(14)**

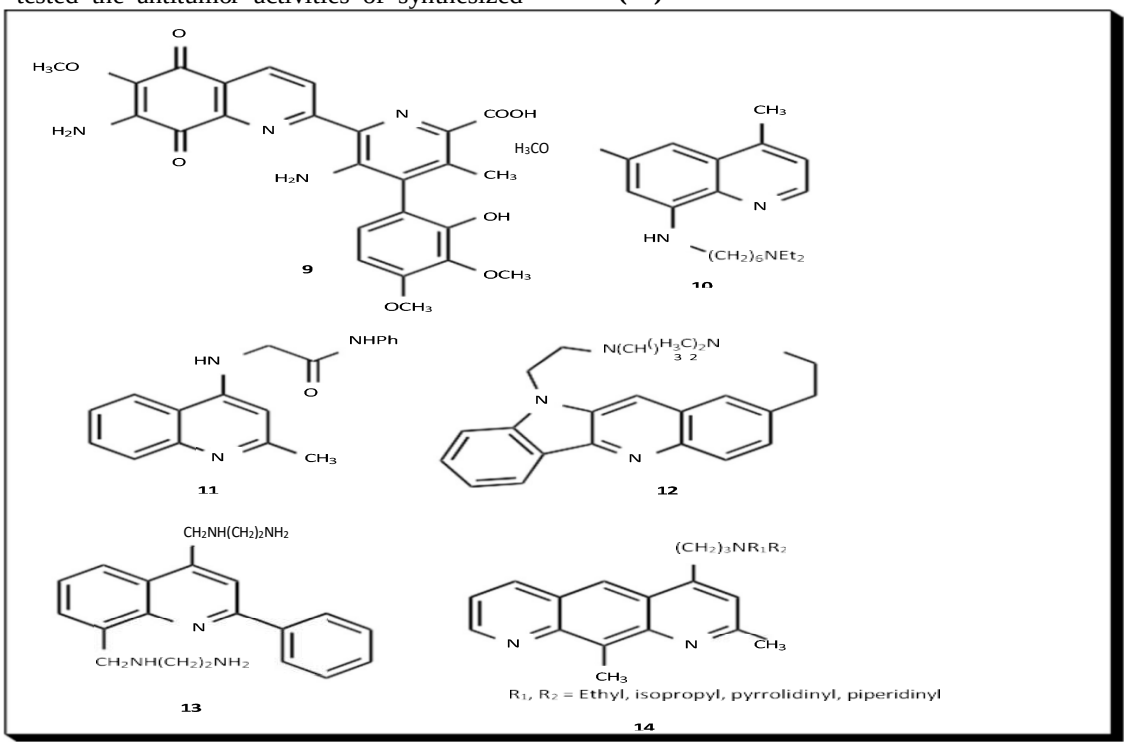

Fig 7: Mechanism of quinoline as anticancer activity

Anti-mycobacterial Activity:
Tuberculosis, a global pandemic causing 2 million deaths annually, is the leading killer epidemic among HIV-infected individuals with weakened immune systems, with 8 million new cases each year Tuberculosis (TB) is a global health issue due to the lack of proper therapeuticagents and the resurgence of TB, especially with HIV and multi-drug-resistant (MDR) strains.The study tested the antibacterial and antifungal activities of synthesized compounds against various bacterial and fungal species. The compounds were tested in vitro using the standard

agar disc diffusion method and compared with ampicillin as a reference drug. The compounds showed varying degrees of inhibition against the tested microorganisms. Compounds 9 and 11 exhibited strong antibacterial activities against Gram negative bacterium Escherichia coli, exceeding the activity of the reference antibiotic ampicillin. Compound 15 showed strong antibacterial activity against Escherichia coli, with double the value of the reference antibiotic used. Compounds 18 and 19 exhibited good inhibitory activity against Escherichia coli, providing valuable results for pharmaceutical and biological control applications. The outer membrane of Gram-negative bacteria, which comprises a complex liposaccharide (LPS), protects them from antibiotics, dyes, and detergents. The study introduces compounds 15, 11,and 9 as effective agents against Escherichia coli and suggests applying pharmaceutical drug tests on them. **(15)**

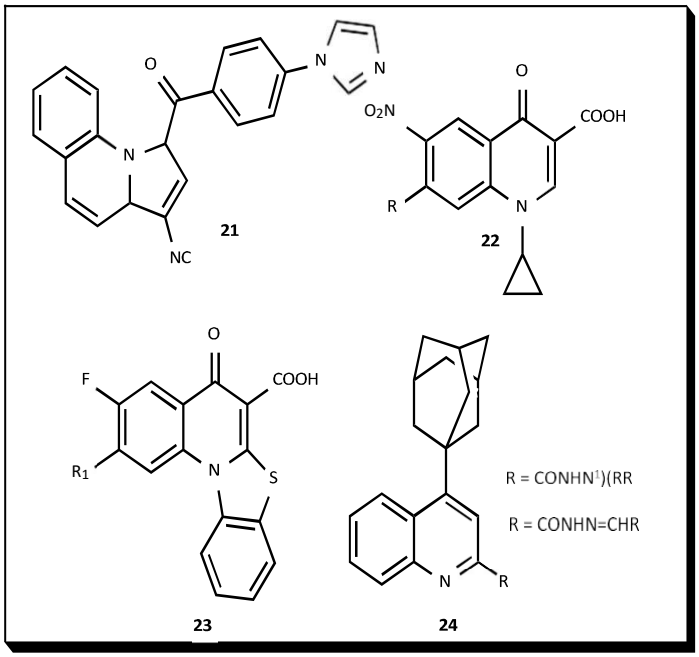

Fig 8: Mechanism of quinoline as Antimycobacterial agents

Anti- Microbial Activity:

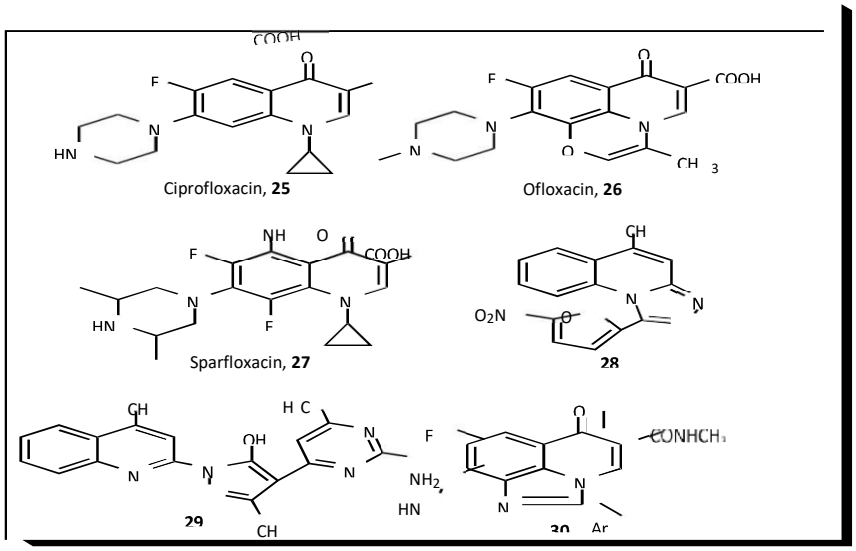

Fig 9: Mechanism of quinolines as Anti- microbial agents

Multi-drug resistant microbial infections have become a significant health concern, making the search for new antimicrobial agents challenging. Quinolones, a special structural class of quinoline antimicrobial agents, have been extensively studied for their antibacterial activity. Some compounds have shown moderate activity against various Gram-positive and Gram with some showing moderate to good activity against various strains of bacteria and fungi. Acetamides analogues of 2-chloro-8-methyl quinoline have also been reported to have antimicrobial activity. The study tested the antibacterial and antifungal activities of synthesized compounds against various bacterial and fungal species. The compounds were tested in vitro using the standard gar disc diffusion method and compared with ampicillin as a reference drug. The compounds showed varying degrees of inhibition against the tested microorganisms. Compounds 9 and 11 exhibited strong antibacterial activities against Gram negative bacterium Escherichia coli, exceeding the activity of the reference antibiotic ampicillin. Compound 15 showed strong antibacterial activity against Escherichia coli, with double the value of the reference antibiotic used. Compounds 18 and 19 exhibited good inhibitory activity against Escherichia coli, providing valuable results for pharmaceutical and biological control applications. The outer membrane of Gram-negative bacteria, which comprises a complex liposaccharide (LPS), protects them from antibiotics, dyes, and detergents. The study introduces compounds 15, 11, and 9 as effective agents against Escherichia coli and suggests applying pharmaceutical drug tests on them. **(16)**

Anti-convulsant Activity:

Epilepsy affects over 60 million people globally. Most available drugs, approved before 1985, provide seizure control for 60-70% of patients. However, they cause side effects, making research for safer anticonvulsant drugs challenging. Epilepsy is a neurological disorder involving abnormal electrical activity in the brain. Animal models like the MES and scPTZ test are used to characterize anticonvulsant activity of new compounds. Recent molecular modifications of quinoline derivatives have shown promising anticonvulsant results. Quan et al. reported a series of 5-alkoxy-triazolo[4,3-a]quinoline derivatives with potent anticonvulsant activity. Quan extended their work to synthesize 7-alkoxy-4,5-dihydro-triazolo[4,3- a]quinoline-1(2H)-dihydro-[1,2,4]thiazolo [4,3-a]quinoline-1(2H)-one. Fused triazole and triazolone derivatives of quinoline-2(1H)-one showed stronger anticonvulsant effects. **(17)**

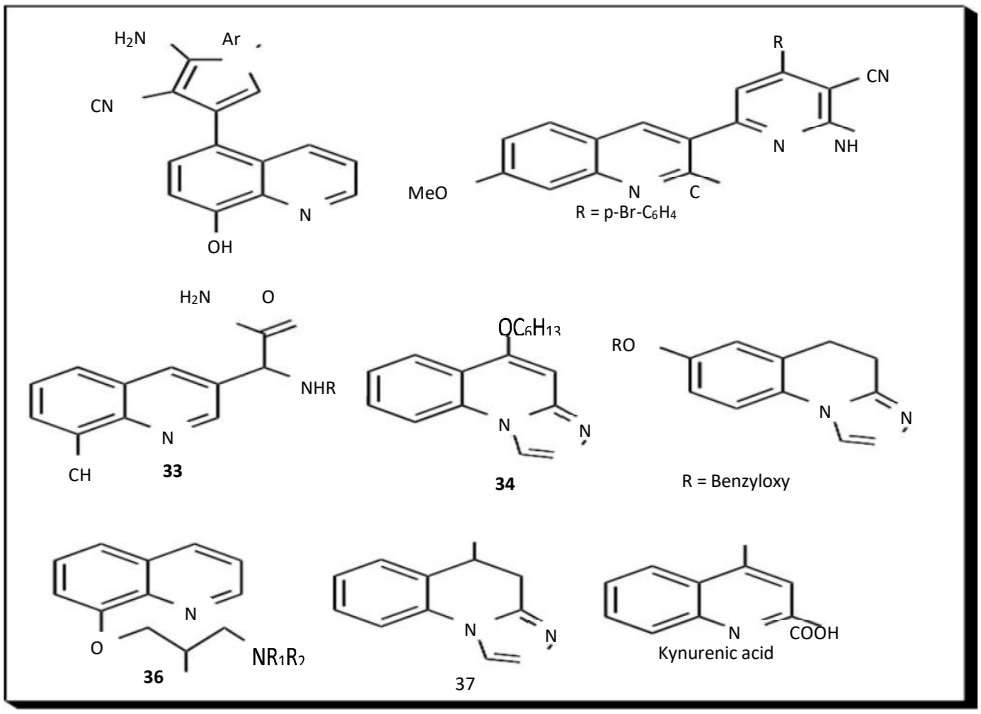

Fig10: Anti-convulsant activity of quinoline

Cardiovascular Activity:
Researchers have been exploring potential cardiovascular agents like calcium channel blockers and cAMP phosphodiesterase III through chemical modifications of quinoline derivatives. Some compounds have shown hypotensive effects in animals, while others have shown cardiovascular activity on isolated hearts. Mannich bases prepared by aminoalkylation of quinoline showed vasorelexation in the presence of propanolol. New alkyl 4-(2-fluoro-3- chloro-5-trifluoromethyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates and 9-(3-chloro-2-fluoro-5-trifluoro-methylphenyl)-6,7-dihydrofuro[3,4-b]quinoline-1,8-diones were also developed. Various compounds with pyridazinone moiety have shown vasodilator activity on rabbit hearts.Biarylether amide quinolines, phenyl acetic acid-based quinolines, 4- Thiophenyl quinolines, angiotensin II receptor antagonists, centhaquin, tetrahydroquinolines, and tetrahydroquinolinamines are various agents used in treating dyslipidemia, arteriosclerosis, hypocholesterolemia, angiotensin II receptor antagonists, and platelet aggregation. These agents have good binding affinity for LXRb and LXRa receptors, act as hypotensive agents, and reverse conditions of arteriosclerosis. Some compounds have shown positive results, such as losulazine, which has hypotensive effects in various animals. Other compounds have shown cardiovascular activity on isolated hearts, and some have been designed as structurally analogues of 1,4-dihydropyridines. Some compounds have also shown moderate vasorelaxantactivity compared to standard drugs like Milrinone. These studies aim to identify potential cardiovascular agents and develop new lead compounds. **(18)**

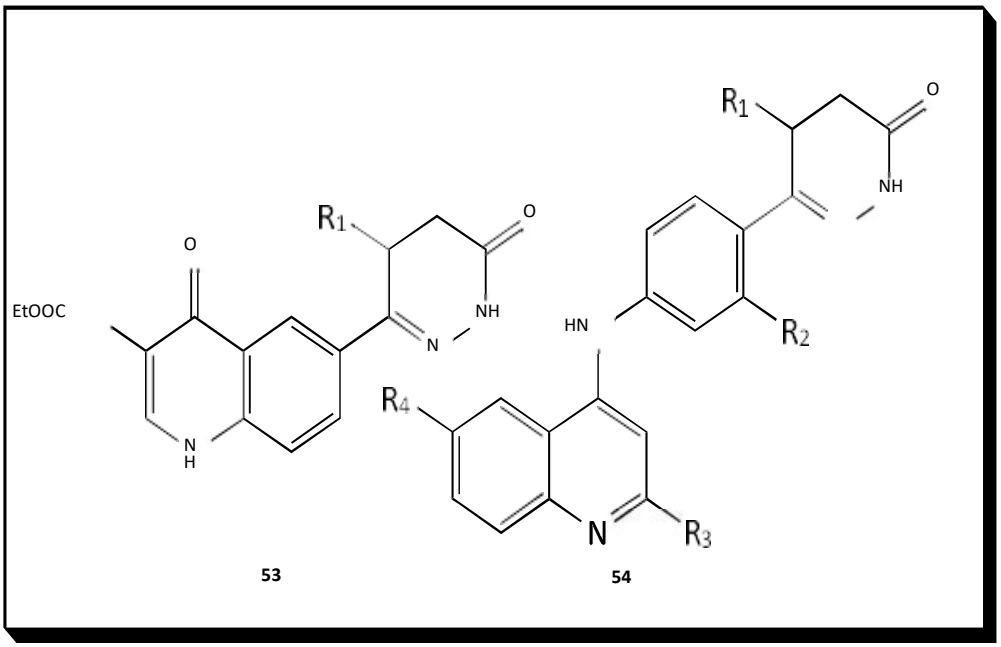

Fig11: Cardiovascular activity of quinolines

Anti-malarial activity:
The quinoline ring has significant antimalarial potential, with bisquinolines, analogues of ferrochloroquine, 7-chloroquinolinyl thioureas, ureido-4-quinolinamides, chloroquinolyl derivatives, 4-aminoquinoline triazines, 5-aryl-8-aminoquinolines, pyridine-quinoline hybrids, and 4-anilinoquinoline ring compounds showing good activity against chloroquine-sensitive P. falciparum strains and rodent malaria parasite P. yoeii. These compounds have shown promising results against both chloroquine-resistant and chloroquine-sensitive parasites in vitro models. Quinine has rapid schizonticidal action against intra-erythrocytic malaria parasites. It is also gametocytocidal for Plasmodium vivax and Plasmodium malariae, but not for Plasmodium falciparum. Quinine also has analgesic, but not antipyretic properties.

The quinoline-containing antimalarial drugs, chloroquine, quinine and mefloquine, are a vital part of our chemotherapeutic armoury against malaria. These drugs are thought to act by interfering with the digestion of haemoglobin in the blood stages of the malaria life cycle. **(19)**

Anti-inflammatory activity:
Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for treating inflammatory and painful conditions like rheumatoid arthiritis, soft tissue and oral cavity lesions, respiratory tract infections, and fever. Various aryl or heteroaryl acetic acid derivatives have been used fortheir anti-inflammatory activity. Recent research has synthesized various 4–hydroxyquinoline derivatives and 8–(phenylmethylene)tetrahydroquinoline analogues, with some showing analgesic and anti-inflammatory properties. These compounds have also been studied for disease-modifying anti-rheumatic drugs (DMARDs) and their ability to inhibit the formation of Leukotrienes via the 5–lipoxygenase enzyme. **(20)**

CONCLUSION:

Quinoline derivatives are crucial in organic synthesis and medicinal chemistry. Researchers have synthesized hybrid quinoline scaffolds using metal-free, ionic liquid, and ultrasound irradiation procedures. These methods meet green chemistry requirements. Researchers are now focusing on eco-friendly reaction procedures, such as metal-free, solvent-free, aqueous media, and ionic liquid catalyzed reactions. Quinoline and its derivatives have potential applications in treating human infections like bacterial, cancer, malaria, and fungal infections. Researchers have synthesized quinoline and its fused heterocyclic derivatives, leading to the development of new quinoline derivatives with various biological activities, including anticancer, antimicrobial, anticonvulsant, anti-inflammatory, and cardiovascular activities, offering immense potential for drug development. The study presents an efficient synthesis of a new series of Selenia diazoles and triazolo[1,5-a]quinoline derivatives, which were screened for anticancer and antimicrobial activities. Some compounds showed strong inhibitory effects against breast cancer, moderate cytotoxic activities against cell lines, and moderate activity against phytopathogenic fungi and Gram positive and Gram negative microorganisms. Compounds 4-17 displayed strong antifungal activities, with compounds 4 and 17 being more potent against Fusarium sp. and Rhizoctonia sp.

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