International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 8s, 2025
https://theaspd.com/index.php

Novel Synthetic Approaches and Biological Evaluation of Quinoline Derivatives for Antimicrobial Resistance

Manikandan Sankaran[1]
Department of Chemistry, Hindustan College of Science and Technology, Padur-603103, (Tamil Nadu) India
Kiruthiga Kaliyamoorthy[2]
Department of Chemistry, Hindustan College of Science and Technology, Padur-603103, (Tamil Nadu) India
Corresponding Author: manigomathi89@gmail.com and kkiruthiga@hindustanuniv.ac.in

Abstract: *As Quinoline derivatives exhibit various mechanisms of action such as DNA synthesis inhibition, membrane integrity disordering, and reactive oxygen species generation, they become important agents in the battle against antimicrobial resistance. The present review focuses on the importance of quinoline derivatives in combating antimicrobial resistance, as well as summarizes the key structural attributes responsible for their potency and discusses Structure-Activity Relationship (SAR) studies important towards tailoring these scaffolds. Highlights of the study involve the discovery of crucial substituents, hydrophobicity, and electron supply effectiveness in augmentation to antimicrobial activity and opportunities for new SAR approaches to find novel medications.*

Keywords: *Synthetic Approaches, Biological Evaluation, Quinoline Derivatives, Antimicrobial Resistance*

INTRODUCTION

Antimicrobial resistance (AMR) has become one of the most urgent global health threats, which could compromise modern medicine; that is, it poses major risks for disease treatment as well as general morbidity and mortality. AMR is the consequence of overuse and misuse of antibiotics in humans, animals and agriculture as well as the absence of the development of new antimicrobial drugs. AMR has far-reaching consequences, increasing the incidence of illness and death, as well as healthcare expenditures; AMR is a significant threat to global public health, economic security, and social welfare (Dadgostar, 2019; Morrison and Zembower, 2020). Antimicrobial resistance is the ability of microorganisms such as bacteria, viruses, etc., to resist antimicrobial drugs rendering standard treatments ineffective and infections persist causing more severe diseases. The World Health Organization (WHO) has reported that "Antimicrobial resistance is on the rise in almost every country" (Marston et al, 2016). The Global Antimicrobial Resistance and Use Surveillance System (GLASS) report confirms high levels of AMR across different regions in common bacterial diseases such as urinary tract infections, bloodstream infections, and pneumonia (WHO, 2020). **Major driver**: Misuse of antibiotics (in both healthcare and agriculture), this is what caused AMR. Antibiotics are OTC drugs in many countries, further facilitating their misuse. Additionally, in agriculture, antibiotics are frequently given to animals for growth promotion purposes, leading to a generation of resistant strains that may be passed on by the food chain (Ventola, 2015). This situation is worsened by the lack of strict regulations and monitoring efforts, which permits resistant strains to expand their presence worldwide.

Quinolines Importance in the Fight against AMR:

Given this rapidly advancing background of emerging resistance, there is an urgent imperative to provide new antimicrobial agents. One example of such compounds that are promising candidates is quinoline derivatives. Quinolines are of great interest as they exhibit a wide range of activity against different types of pathogens, i.e., bacteria, fungi, and parasites. Quinolines, especially fluoroquinolones, act by inhibition of bacterial DNA gyrase and topoisomerase IV, which are necessary for bacterial cell replication/transcription (Hooper et al, 2001). This prevents the process of bacterial DNA and hence results in cell death. Both targets of the drug rivet greatly reduce resistance formation and consequently quinolines are highly effective against almost all pathological bacteria.

Activity With Respect to Resistant Strains: Quinolines have shown notable activity against multiply resistant (MDR) strains. For example, Ciprofloxacin, a fluoroquinolone, has activity towards many Gram-negative bacteria such as Pseudomonas aeruginosa and Escherichia coli (Van Bambeke et al., 2005) again these notoriously resistant species. It is especially desirable in healthcare settings, where MDR infections are increasingly common and difficult to treat with conventional antibiotics, for quinolines. There are

more than just anti-bacterial infections using quinoline derivatives. For instance, Chloroquine and Hydroxychloroquine have been clinically used to treat malaria - a parasitic infection due to Plasmodium falciparum. (Al-Bari, 2015). Their role in treating malaria has made them vital for areas where the disease is endemic; even more, these molecules may be used to cure other diseases like autoimmune reactions and viral illnesses. (Ben-Zvi et al, 2012)However, quinolines are not free from challenges despite their effectiveness. This would lead to the development of newer derivatives and combination therapy using new compounds for containing quinoline-resistant strains, which emerge as an important barrier in vivo (Piddock, 1999). In addition, the risk for adverse events, including tendonitis and neurotoxicity, dictates the judicious application of these agents with vigilant monitoring (Alves, Mendes, & Marques, 2019).The research on new quinoline derivatives is vivid while the molecules are still under chemical modifications to enhance their potency, mitigate toxicity, and bypass resistance mechanisms as well. E.g., the more recent development of advanced fluoroquinolines seeks to improve activity against Gram-positive pathogens and anaerobes, widening indications within this antibiotic class (Dalhoff 2012).Relative efficacy of quinoline derivatives to other classes of antibiotics-Fluoroquinolones, a group of quinoline derivatives, are widely known to have broad-spectrum antimicrobial activity and an uncommon mechanism of action against bacteria compared with other antibiotic classes. Fluoroquinolones act indirectly against bacteria as well by the inhibition of two enzymes required for bacterial DNA replication and transcription, known as topoisomerase II (DNA gyrase). A primary mechanism encompasses these fluoroquinolone activity targets within prokaryotic cells. The dual-target approach not only makes them more bactericidal but also less likely to promote the emergence of resistance than an antibiotic that acts on just one bacterial process. Quinoline derivatives are better against Gram-negative bacteria, including multidrug-resistant strains such as Pseudomonas aeruginosa and Escherichia coli, than the β-lactams, which inhibit cell wall synthesis (Van Bambeke et al., 2005). The ability of β-lactams to inhibit cell wall biosynthesis makes them a highly effective class for the treatment of Gram-positive organisms, but their activity against bacteria with an outer membrane is frequently compromised by periplasmic and type II (ESBLs) or IIIb extended spectrum β-lactamases that degrade this antibiotic.Macrolides and tetracyclines, focusing on protein synthesis, are the second principal group of antibiotics. They are typically broad-spectrum agents; however, their rapid resistance development and slow bacteriostatic rather than cidal action limit their clinical use (Kohanski et al., 2010). On the other hand, quinoline being bactericidal ensures faster and efficient eradication of infections. That quinoline derivatives have antimalarial properties are known from the work on Plasmodium owing to chloroquine and hydroxychloroquine (Ren et al., 2020), therefore they may be of general use against infectious diseases. This very wide spectrum contrasts with the more limited ranges of anti- (against one other bacteria) and -biotic (any bacterium except those in its own kingdom, eukaryota). All in all, quinoline derivatives present themselves as a powerful class of the antibiotic armamentarium by their dual-target and antifouling features, which makes them better than many other antibiotic classes with broad spectrum activity.

CONVENTIONAL SYNTHETIC METHODS

Traditional Approaches to the Synthesis of Quinoline Derivatives and Limitations:

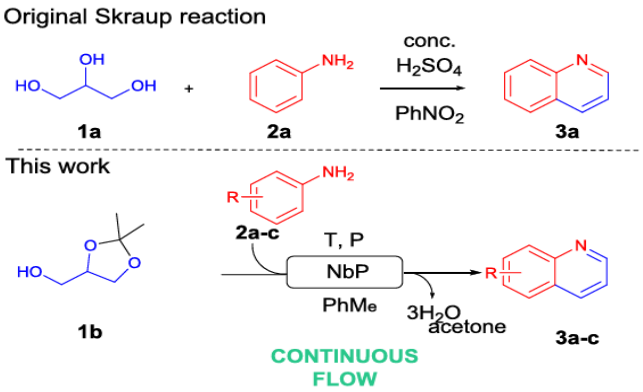
Quinoline derivatives are an important class of heterocyclic compounds that display a wide range of applications including medicinal chemistry, agricultural chemicals, and materials science. Their preparation has been studied extensively, leading to many archaic syntheses established upon traditional methodology. Traditional methods typically associated with these practices are often encumbered by many challenges that can hinder their effectiveness, sustainability, and ecological friendliness.

Classical Synthesis Methods

1. Skraup Synthesis:

One of the original approaches to synthesizing quinolines is the Skraup synthesis, which entails cyclizing aniline with glycerol in combination with a powerful oxidant such as nitrobenzene or arsenic acid. Reactant sulfuric acid is usually used as a catalyst and the reaction proceeds exothermically.

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 8s, 2025
https://theaspd.com/index.php

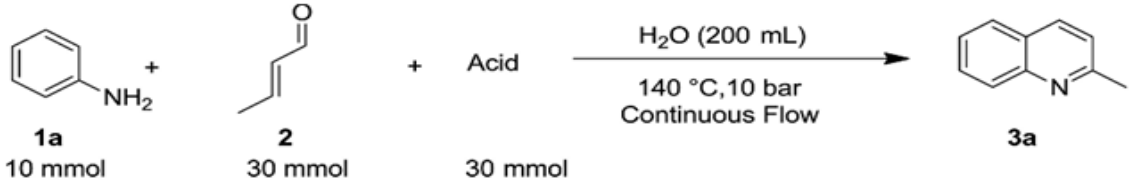


Scheme 1. Original Skraup reaction[13] and the continuous flow Skraup reaction of solketal **1b** and anilines **2** over niobium phosphate (NbP) described in this paper.

Scheme1: Source- Jin, J., Guidi, S., Abada, Z., Amara, Z., Selva, M., George, M. W., & Poliakoff, M. (2017). Continuous niobium phosphate catalysed Skraup reaction for quinoline synthesis from solketal. *Green Chemistry*, *19*(10), 2439-2447.

2. Doebner-Miller Synthesis:

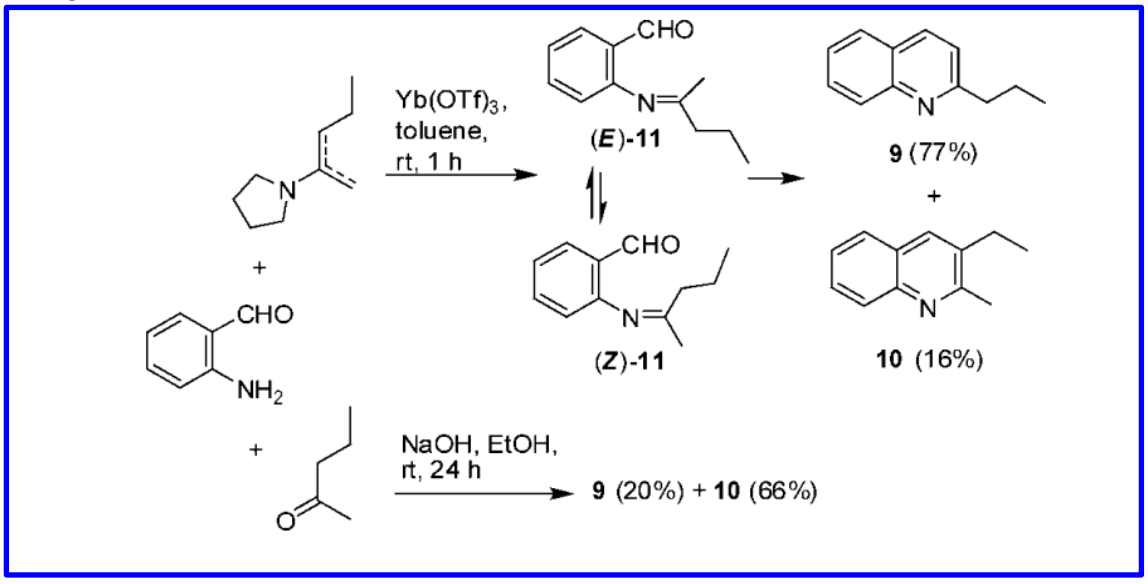
The Doebner-Miller synthesis is a well-known historic pathway in which aniline reacts with α, β-unsaturated carbonyl compounds using acid catalysts. The approach is particularly good for the preparation of 2-substituted quinolines.



Scheme2: Source- Yalgin, H., Luart, D., & Len, C. (2016). First examples of Doebner-Miller reaction in flow: Efficient production of 2-methylquinoline derivatives in water. *Journal of Flow Chemistry*, *6*(2), 80-85.

3. Friedländer Synthesis:

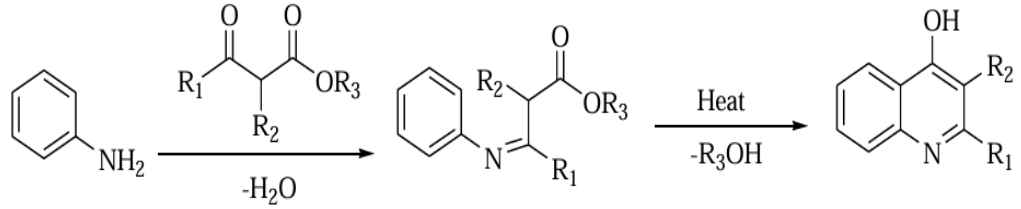
The Friedländer synthesis was first described in 1882 and involves the condensation of 2-aminobenzaldehyde with a carbonyl compound containing an active methylene. The approach developed here is very efficient, allowing the direct construction of a variety of substituted quinoline derivatives throughout this manner.



Scheme 3: Friedlander Reaction of 2-Amino Benzaldehyde with 2-Pentanone (Source: Marco-Contelles, J., Pérez-Mayoral, E., Samadi, A., Carreiras, M. D. C., & Soriano, E. (2009). Recent advances in the Friedlander reaction. *Chemical reviews*, *109*(6), 2652-2671.

4. Conrad-Limpach Synthesis:

In a synthesis of 4-hydroxyquinoline, Fenamic acid is produced from aniline and β-ketoesters under acidic or basic conditions. The intermediates are even extra trans-log by modification in different ways to the various quinoline derivatives.



Scheme 4: Conrad-Limpach quinoline synthesis

Challenges in Traditional Synthesis:

Although traditional procedures for the synthesis of quinoline derivatives have been developed, hurdles are associated with this method:

Harsh Reaction Conditions: Several conventional protocols for the synthesis quinoline demand chemically harsh conditions, usually involving high temperatures and strong acids/bases or toxic reagents. Sulfuric acid and nitrobenzene are used in the Skraup synthesis, however these reagents present difficulties with regard to handling and disposal due to their corrosive properties (Sidebotham & Seyden-Penne 1997).

Low Selectivity and Yields: In turn, traditional methods tend to have poor selectivity and low yields. The Skraup synthesis is an example where the formation of by-products from side reactions leads to difficulty in purification (Taylor & Katritzky, 2005).

Appearance and Security Issues: Conventional synthesis methods are associated with significant environmental and safety issues due to the use of toxic reagents and solvents. Nitrobenzene and arsenic acid are reagents that can be harmful to people, animals, and the environment. The requirement for high acidic or basic when working with AOs also results in some significant acid/base waste which needs caution treatment (Tanaka, 2002).

Scalability Issues: The conversion of traditional synthetic methods from laboratory to industrial scale may present difficulties. Certain reactions, e.g., the Skraup synthesis are highly exothermic and end up as potential runaway reactions with difficulty on a larger scale in terms of process control (Mittal et al, 2023).

Functional-Group Tolerance: Various classical methods inherently suffer from poor functional group tolerance thereby limiting the diversity of quinoline derivatives that can be synthesized. This weakness is especially apparent in medicinal chemistry applications where the addition of a variety of functional groups at once represents an optimization hotspot with regards to biological activity (Patel et al. 2022).

Green Chemistry and Modern Approaches: These diversions are a consequence of the abysmal atom- and step-economies associated with traditional synthetic methods, prompting significant research efforts towards orthogonal strategies that enable accelerated development without compromise to selectivity or waste-product generation. These include as discussed below:

Microwave-Assisted Synthesis: It is typically faster and can give higher yields, which often require milder conditions than traditional methods. It is also environment-friendly, and further it improves the energy efficiency of the synthesis process (Kappe 2004).

Ionic Liquids and DES: Application of ionic liquids and deep eutectic solvents as reaction media can improve the selectivity and efficiency in quinoline synthesis. These solvents are generally less toxic and more environmentally friendly than traditional organic solvents, supporting the tenets of green chemistry (Welton 2004).

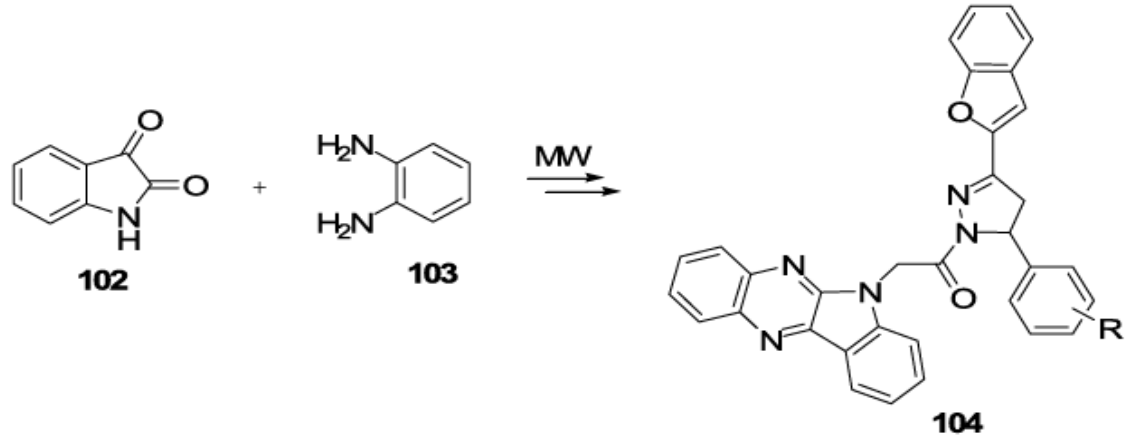
Catalyst Development: Recent advances in developing new catalytic systems such as heterogeneous catalysts, and metal-organic frameworks (MOFs) have enabled the synthesis of quinoline derivatives via

alternative routes. Catalysts may also offer improved selectivity and reusability, which in turn would lead to reductions in the amounts of stoichiometric reagents required enabling the reduction of waste (Tombesi, & Pettinari, 2021).

Flow Chemistry: It has a clear advantage in obtaining control over reaction parameters and facilitates the safety, compactness, and scalability of quinoline synthesis. One common factor is in-line purification steps, such as chromatography that is frequently used downstream of batch processes but can be incorporated directly into continuous flow systems (Plutschack et al., 2017).

Although traditional methods for the construction of this pharmacologically important framework have been well-established and provided a solid base in organic synthesis, they are typically hindered by numerous drawbacks such as harsh reaction conditions, low selectivity, environmental/safety issues, scalability problems, and limited functional group tolerance. This shortcoming can be addressed via modern synthetic approaches and by the use of green chemistry principles, allowing obtaining more efficient, selective as well as environmentally-friendly alternatives. The improvement of synthetic methodologies will certainly broaden the popularity and use of quinoline derivatives in a multifaceted direction.

MICROWAVE-ASSISTED SYNTHESIS



Scheme 5: Synthesis of 2- [1-(5,8-dihydro Quinoxalino[2,3-b] Indoloacetyl)-3-(1-benzofuran-2-yl)-4,5-dihydro-1H-pyrazol-5-yl] phenyl derivatives. (Source: Majumder, A., Gupta, R., & Jain, A. (2013). Microwave-assisted synthesis of nitrogen-containing heterocycles. *Green Chemistry Letters and Reviews*, *6*(2), 151-182. Microwave-assisted organic synthesis (MAOS) has become a prominent technique in modern chemistry due to its ability to significantly enhance reaction rates, yields, and selectivity compared to conventional methods. This is particularly true for the synthesis of quinolines, a class of heterocyclic compounds with broad applications in medicinal chemistry, agrochemicals, and materials science. The principles and advantages of microwave-assisted quinoline synthesis, along with the key optimization parameters such as temperature, reaction duration, and solvent selection, are discussed herein. Microwave-assisted reaction can be guided by microwave principles in curing or drying applications. The most important basic principle of MAOS is the ability to heat up reaction mixtures effectively via microwave irradiation. Microwaves are basically electromagnetic waves falling within a frequency-band of 300MHz-30 GHz and with wavelengths pertaining to those frequencies from one meter down to one millimeter. They oscillate polar molecules (water, say) and ionic species in a reaction mixture to generate heat via dielectric heating. This results in a fast and even heating of the reaction mixture, making it typically more efficient than conventional conductive heating methods (Kappe et al., 2004). In the case of quinoline synthesis, microwave exposure can supply energy to reactants and intermediates so that any cyclization or condensation reaction necessary for its core assembly takes place within this framework. In

contrast to conventional thermal methods, this strategy frequently provides higher reaction rates and yields. Benefits of a Microwave-Assisted Quinoline Synthesis Rapid Reactions and Increased Yields - Microwave-assisted reactions usually exhibit higher reaction rates leading to faster time for the reagents at a certain temperature resulting in greater yields. This is especially useful for the synthesis of complex heterocycles like quinolines which pass many steps and intermediates. For example, what are usually long and tedious works may be accomplished in minutes using microwave-assisted Povarov reactions for the synthesis of quinolines (Varma, 1999).

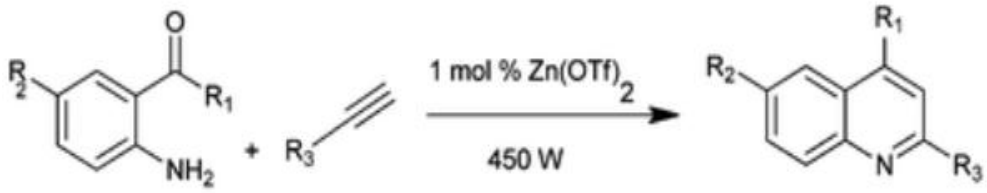
Energy Efficiency: direct heating to the reaction medium avoids energy waste for it is not necessary heat an entire surrounding space as well as their own cooking container. This is a more efficient and ecofriendly way of the process. Selective Cleanliness: The microwave-assisted method of synthesis is reported to be particularly useful when it comes down the control which situations occur. This generally leads to more pure final products and thus less need for long purification sequences (Kappe 2004).

Scalability: The development of microwave technology makes the large-scale quinoline synthesis through microwaves (Leadbeater, 2008). Optimization Parameters

Temperature: The reaction temperature is an important parameter in microwave assisted synthesis. Microwaves differ from conventional heating in that they can quickly attain much higher temperatures, allowing them to effect reactions far faster. However, it is important to have control of the reaction in order not degrade reactants or products. Quinoline synthesis, for example, generally requires a temperature in the 100–200°C range depending on reaction and substrates (Kappe et al., 2004) Microwave-assisted reaction shortened the time of preheating stage by almost half. The reaction times can be decreased (from hours to minutes). That is, Povarov-odd metal trivalent species typically exhibit ultrarapid reaction kinetics and hence permit full cycloaddition conversion in less than 30 minutes where a conventional duration could easily run to several hours. The best response time should be figured by trying different things with various reaction times 190 to find harmony between the completion of reactions and escape from side responses (de Paiva et al, 2022)

Solvent selection: Solvents are one of the key parameters which affect efficacy in microwave-assisted synthesis and subsequently reaction outcomes. Polar solvents are suitable polar hydrogen bonding interactions, such as ethanol, methanol and water have high dielectric constants hence group insertions could be efficiently microwaved. Non-polar solvents like hexane on the other hand are more ineffective and is generally not used in microwave reactions. It is more environmentally friendly and the product isolation can be simplified as well in some cases because solvent-free conditions are used.

Catalytic Systems



Scheme 6: Quinoline derivatives were synthesized by employing amino acetophenone and phenylacetylene in the presence of Zn $(OTf)_2$ as an effective catalyst under microwave irradiation. (Source: Prajapati et al, 2014)

Catalysts are implemented in many industries and various chemical reactions because it helps the rate at which a chemical reaction occurs without being used up. From the aforementioned systems, metal-organic frameworks commonly abbreviated as MOFs have attracted keen interest resulting from their structural versatility and the attraction of large surface area. MOFs consist of metal ions or clusters connected by organic ligands to build up one-, two- or three-dimensional networks. Due to the possibility of adjusting their structure for desired pore size and shape, and the functionalization of the organic and inorganic building blocks, MOFs are very promising in catalytic processes for the preparation of quinoline derivatives.

As mentioned earlier, there are many mechanisms and advantages linked to the use of catalytic synthesis in the production of Quinoline derivatives. Quinoline derivatives are one of the essential heterocyclic compounds that can be used extensively in pharmaceuticals, agrochemicals, and organic materials. The MOFs based synthesis of quinolines has several methodologies associated with it where majorly, the high area of the MOFs and the ability to change the pore environment to the maximum possible extents is made use to control and optimize the reactions. Here, it is looked at the working principles and benefits of employing MOFs for this role.

Mechanistic Pathways:

Lewis Acid Catalysis: This invariably makes the use of small organic molecule catalysts – such as metal-organic frameworks (MOFs) for the synthesis of quinoline derivatives possible and practical through one of the pathways outlined below. Most of the MOFs contain metal nodes including Zn, Cu, Fe, and so on, these Metal nodes as a Lewis acid site can activate the carbonyl groups or nitriles to get ready for the nucleophilic attack by amines or any nucleophiles. This activation reduces the activation energy and thus raises the rate of the reaction.

Brønsted Acid Catalysis: Among the MOFs, those with the specific pore structures can bear additional functional groups which can make the MOFs as Brønsted acid catalysts including sulfonic acid groups. These sites can protonate intermediates; stabilize transition states helping in the formation of quinoline derivatives. This bimodal catalytic behavior can be felt at a plus in multiphase synthetic routes, where both types of acidic sites are desirable.

Hydrothermal and Solvothermal Synthesis: MOFs are typically used under hydrothermal or solvothermal conditions, these conditions entail a high-pressure high temperature environment that is suitable to the formation of quinoline derivatives. Basically, the MOFs have open-framework structures, and this is facilitating the diffusion of the reactants toward the active sites, thereby making the catalytic performance to be improved.

Photocatalysis and Electrocatalysis: Some of the MOFs with photoactivity and/or electro activity can perform the catalytic reactions under light and/or electrical inputs. For example, utilizing MOFs with Ti or Zn nodes is capable of absorbing the light and producing electron hole pairs which are necessary for the redox reactions for synthesis of quinoline derivatives. In the same way, electrocatalytic MOFs can help improve electron transfer reactions because the effective catalyst cycle is also an issue here.

Advantages of MOF Catalysts:

High Surface Area and Porosity: MOFs have very large porosity, the size of the pores can be easily adjusted and they offer several reactive sites, as well as diffusivity of the reactants and products. This characteristic greatly improves the direct synthesis and choosing action of MOFs in the preparations of quinoline derivatives.

Tunability and Functionalization: As shown in this MOFs' structures are scalable and can accommodate different functional groups and metal ions, which lends itself nicely for optimizing catalytic behavior for certain selected reactions. This flexibility allows the design of MOFs with the most amount of Lewis or Brønsted acid sites, photoactive sites, or any other catalytically active sites.

Stability and Reusability: MOFs are normally chemically and mechanically robust even at high temperatures and or pressures that may be desirable in catalytic reactions. Also, MOFs can be recycled and reused several times without a sharp decline in performance, and this fact makes them financially profitable for the implementation in industries.

Selective Catalysis: As mentioned earlier, the pore size of MOFs can be accurately tuned, which gives place to the selective catalysis, in which only certain reagents can get access to the catalytic sites. This selectivity can be highly beneficial in particular instances such as in multi-step organic synthesis where the selective formation of a product could help avoid side reactions and increase yield.

Environmental and Economic Benefits: Catalysis involving MOFs can also be more efficient and selective over the conventional chemical reactions hence use of excess reagents is minimized and the quantities of wastes produced are small. This green chemistry approach complies with sustainable development objectives as well as this approach can offer tangible source and energy cost savings.

Applications: Some of these include the following; various researches have shown that MOFs can be used for the catalyst synthesis of quinoline derivatives. For example, Fe-based MOFs have successfully been used for the Fischer–Friedländer synthesis of quinolines. These catalysts offer high demand and distinctiveness at comparatively low temperatures confirmed by several works, including Furukawa et al., 2013. In the same way, Cu based MOFs have been used in the A3 coupling reactions for synthesizing quinoline derivatives having superior catalytic efficiency and reusability (Janiak & Vieth, 2010).

Similar example is the employment of Zn-based MOFs in photoredox catalytic quinoline formation. These MOFs are highly efficient photocatalysts for visible light-driven redox reactions for the synthesis of several quinoline derivatives (Dhiya, Monga, & Sharma, 2021). This approach improves the synthesis through better yield but also incorporates the utilization of renewable energy sources, which is one of the principles of green chemistry.

Therefore, the metal-organic frameworks (MOFs) are the efficient and versatile catalyst for preparing the quinoline derivatives. Due to their high surface areas, tunability and stability, they are highly appropriate for different catalytic processes including the Lewis and Brønsted acid catalysis, hydrothermal and photocatalytic reactions. The efficiency of MOFs in catalytic processes does not only include better reaction rates and selectivity, but also numerous environmental and economic benefits. Thus, future advancements in the area of synthesis and characterization of these MOFs are expected to unlock new realms of MOFs use in organic synthesis as well as catalytic industries.

Screening Protocols:

Knowing the multidrug-resistant (MDR) bacteria is a major threat to the health of people, experimental setup for screening potential antimicrobial compounds is necessary. In vitro methods are commonly used to screen the compound library containing potential antibacterial agents while in vivo models can show the compound activity against MDR bacteria as well as the exact mode of action.

In Vitro Assays: Original identification of prospective antimicrobial agents can be carried out using in vitro assays because they are easy to undertake, cheap, and allow the researcher to maintain strict controls. The common types of these assays used are disk diffusion, broth dilution, and agar dilution methods.

1. Disk Diffusion Method: In this method, small disks containing the antibiotic of interest are placed on AGAR plates that have been seeded with the bacterial species of interest. The area around the disk is compared in order to assess the ability of the bacterium to combat the antibiotic (Bauer et al., 1966). This method is quite cheap and easy to implement; however, it results in offering purely qualitative data.

2. Broth Dilution Method: This quantitative method involves growing bacteria in serial dilutions of antibiotics in a liquid culture. MIC is the lowest concentration of the antimicrobial agent at which bacterial growth can no longer be observed as in visible turbidity (Wiegand, 2008). This method is technically more intricate than disk diffusion and can be adopted to the standard robotic format for screens.

3. Agar Dilution Method: As in broth dilution, dilutions of antibiotics in solutions are added to the agar plates. The MIC is expressed as the least concentration of the test compound where there is no visible bacterial growth on the agar-media surface (Balouiri, 2016). Also, it is considered beneficial in assessing the activity of a number of compounds affecting different bacteria at once.

Further, the checkerboard assay and time-kill assay can also be carried out in vitro which give better and clearer findings on the interaction between antibiotics and bactericidal activity of antibiotics (Hsieh et al., 1993).

In Vivo Models: As far as the antimicrobial activity is concerned, in vitro assays are useful for the primary screening of antimicrobial agents, however, in vivo models are vital for profiling the therapeutic efficiency of prospective antimicrobial agents in a more physiological environment. In vivo models assist in estimating the pharmacokinetics, toxicity and effectiveness against MDR bacteria with in a host organism.

1. Mouse Models: Mice are used due to their genetic relation to humans and multiple available options of genetically modified animals. Systemic models, for example, sepsis, and localized such as pneumonia enable one to study the interaction and effectiveness of antibiotics and the immune system in the host (Hancock, 2005).

2. Galleria Mellonella: These larvae of the wax moth have, therefore, transformed into mammal models' better substitutes. It also has a natural immunity like the mammals and can effectively be used to determine the ability of MDR bacteria on their host and the effectiveness of the antimicrobial agents (Desbois & Coote, 2011). This model is inexpensive, socially acceptable and is amenable to high volume / low-cost screening.

3. Zebrafish Embryos: We have used zebrafish embryos because they are non-mammalian, transparent and their genome can be manipulated easily to analyse bacterial infections and effects of drugs in living organisms. Given that they are small-sized and develop very fast, they are ideal for HTS and real time imaging of infection processes (Prajsnar et al., 2008).

Hence, utilizing both in vitro assays and in vivo models is a holistic strategy in the testing of antimicrobial agents against MDR bacteria. Although screening can be completed rapidly and at a large scale using in vitro tests, the efficacy or safety of the substance cannot be tested in a living organism through in vivo tests. This forms the basis of integrating the various approaches which will enable the development of new antibiotics for use against the emerging MDR bacteria.

Structure-Activity Relationship (SAR)

Structure-Activity Relationship (SAR) studies play a critical role in drug discovery, particularly in optimizing the antimicrobial effectiveness of compounds. By examining the relationship between the chemical structure of a molecule and its biological activity, SAR studies help identify the key molecular features that enhance or reduce antimicrobial properties. This is particularly significant for quinoline derivatives, which have been extensively studied for their antimicrobial potential. Importance of SAR Studies SAR studies are crucial in the optimization of quinoline derivatives for enhanced antimicrobial activity. These studies focus on optimization of efficacy, identification of key functional groups, reduction of resistance development**.** Fine-tuning molecular structures to maximize antimicrobial activity while minimizing toxicity and side effects (Eswaran, Adhikari, & Shetty, 2009). Identifying functional groups or molecular moieties essential for activity, enabling the design of more potent derivatives (Prajapati et al., 2014). Designing molecules less prone to resistance mechanisms by understanding structural features that contribute to antimicrobial activity (Patel et al., 2012). Key molecular features influencing the activity of quinoline derivatives include the position and nature of substituents, hydrophobicity and lipophilicity, electronic effects, steric factors, and hydrogen bonding potential. These features determine the efficacy of quinoline derivatives by affecting their interaction with microbial targets, membrane permeability, and overall stability (Desai et al., 2017; Chen et al., 2009; Sharma et al., 2015). SAR can help to realize the structure–activity relationship and achieve a rational alteration in all chemical structures of the molecule to increase bioactivity. These studies are crucial for several reasons: These studies are crucial for several reasons:

1. Optimization of Efficacy: SAR investigation enables researchers to optimize the structures of molecules to be effectively antimicrobial with less or no toxicity and side effects (Eswaran, Adhikari, & Shetty, 2009).

2. Identification of Key Functional Groups: SAR studies by progressive alteration outline the functional groups or molecular fragments required for activity, and thus, the preparation of improved members (Prajapati et al., 2014).

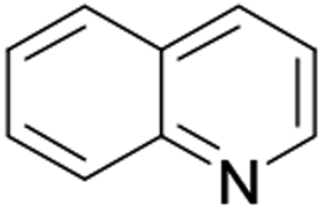
3. Reduction of Resistance Development: That is why the components of the SAR donot contribute to structure features, which may impact on the antimicrobial activity and can be helpful in the designing of the molecules, less susceptible to the resistance mechanisms (Kumar, 2020).

Quinoline derivatives are one of the classes of compounds that possess antimicrobial activity against various types of microbes. The effectiveness of these derivatives is influenced by several molecular features: The effectiveness of these derivatives is influenced by several molecular features. It was observed that there was a variation in the functional group's position in the quinoline ring that determines the antimicrobial efficiency. For example, certain substituents can increase the potency because they organize the electron with microbial targets in definite positions (Desai et al., 2017). It can also be seen that quinoline derivatives are more hydrophobic and lipophilic and this factor determines the penetration of the compounds through the microbial cell membrane. It is stated in literature that with increased

lipophilicity, membrane permeability also increases, but this should be managed by the client's toxicity levels (Chen et al., 2009).

Substituents' electronic effects influence the activity of quinoline derivatives. With regard to electron donating properties, such groups assist in interaction with biological targets; on the other hand, electron withdrawing groups can help in improving stability and selectivity. Influence due to steric hindrance can be peculiar to quinoline derivatives' ability to bind microbial enzymes or receptors. To achieve the high level of antimicrobial effectiveness steric effects should be properly adjusted. Those functional groups that show the hydrogen bond forming ability may increase the binding of Quinoline derivatives with more biological targets leading to better antimicrobial effects (Sharma et al., 2022).

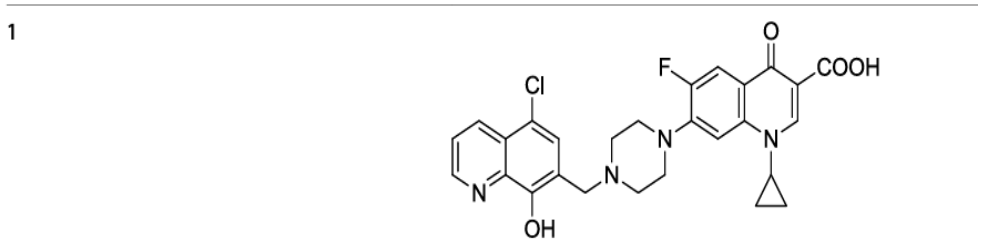
Structure Diagrams: Below are structure diagrams illustrating key molecular features of quinoline derivatives and their impact on antimicrobial activity:



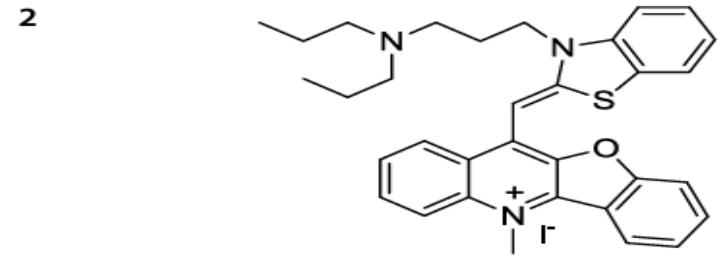
Quinoline 1

Figure1: Basic chemical structure of Quinoline (Source: Weyesa, & Mulugeta, 2020)

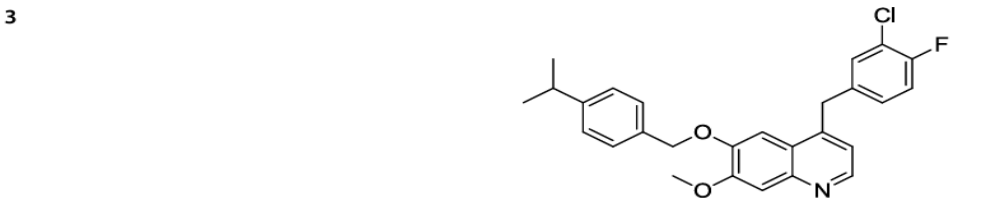
These following diagrams depict the core quinoline structure and variations with different substituents that influence biological activity.



Ciprofloxacin



Methicillin



Daptomycin

Figure 2: Substituted Quinoline Derivatives (1-3 quinoline derivatives are Anti-MRSA or methicillin resistant Staphylococcus aureus active compounds): Source- Kumar, P. (2020). A review on quinoline derivatives as anti-methicillin resistant Staphylococcus aureus (MRSA) agents. *BMC chemistry*, *14*(1), 17.

Antimicrobial mechanisms of quinoline derivatives

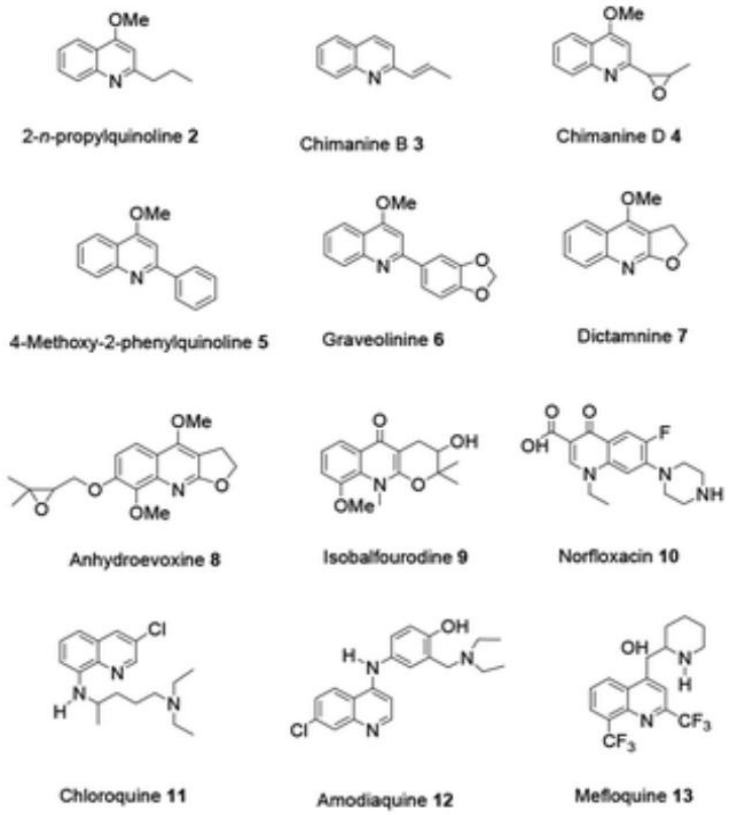


Figure 3: Biologically active Quinoline Derivatives from Natural Sources. (Adapted from Weyesa and Muluget, 2020)

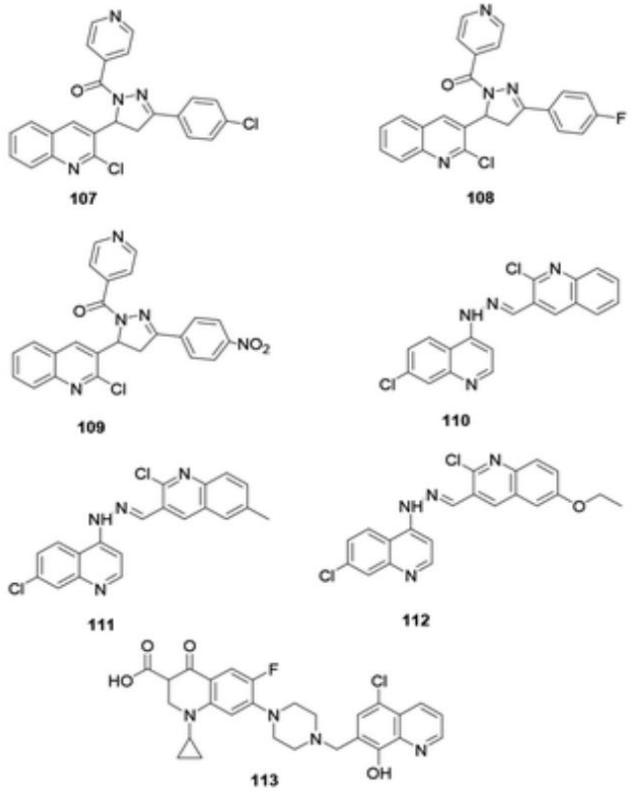


Figure 4: Antibacterial Quinoline Derivatives. (Adapted from Weyesa and Muluget, 2020)

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 8s, 2025
https://theaspd.com/index.php

The most potent antibacterial activity of quinoline derivatives 107, 108, and 109 were synthesized and reported by Desai and colleagues (Fig. 4). Using ampicillin as a reference medication, the synthesized compounds were tested for their antibacterial activity against Escherichia coli, Pseudomonas aeruginosa, Streptococcus pyogenes, and Staphylococcus aureus. Moreover, the authors assert that the substituent effect on the ring is closely related to the compounds' potential activity. Per Le et al., hydrazone is used to link these three bioactive quinoline derivatives. Quinoline derivatives 110, 111, and 112 with a hydrazone linker demonstrated effective growth suppression of the intended bacterium. (Weyesa and Muluget, 2020)

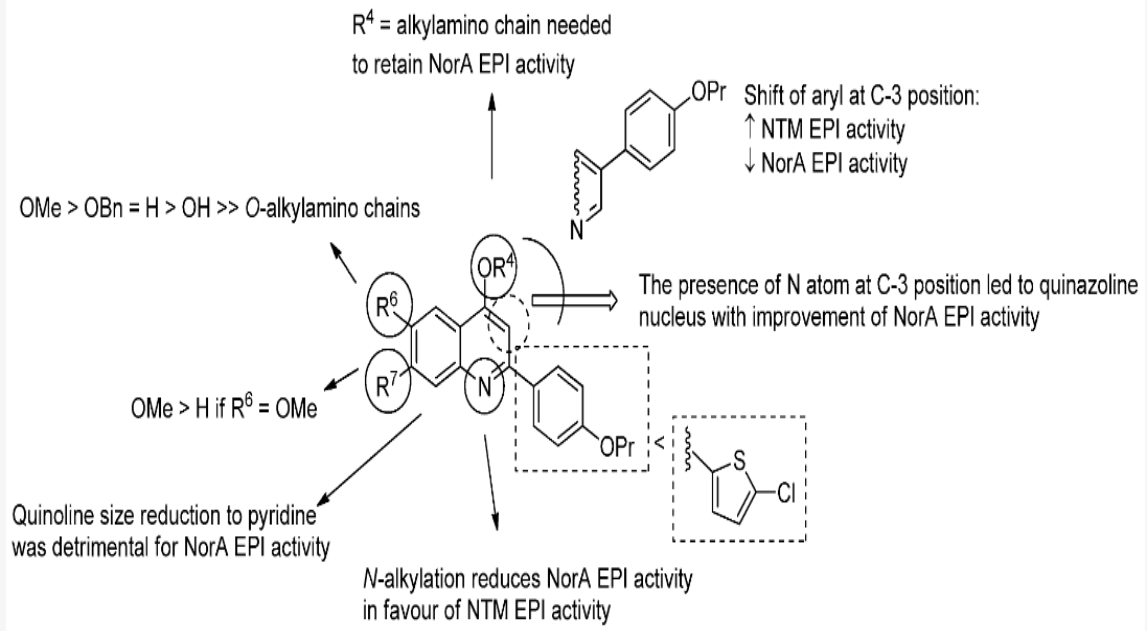


Figure 5: SAR of quinoline derivatives as NorA EPIs. (Source: Cernicchi, G., Felicetti, T., & Sabatini, S. (2021). Microbial efflux pump inhibitors: A journey around quinoline and indole derivatives. *Molecules*, *26*(22), 6996.)

Quinoline derivatives are a significant class of antimicrobial agents, recognized for their broad-spectrum efficacy against various pathogens. The current understanding of their antimicrobial mechanisms highlights several modes of action that disrupt critical biological processes in microbial cells. These mechanisms include inhibition of DNA synthesis, disruption of membrane integrity, interference with protein function, inhibition of nucleic acid synthesis, and generation of reactive oxygen species (ROS).

Inhibition of DNA Synthesis- One of the primary mechanisms by which quinoline derivatives exert their antimicrobial effect is through the inhibition of DNA synthesis. Quinolones, such as ciprofloxacin and norfloxacin, target bacterial DNA gyrase and topoisomerase IV, enzymes essential for DNA replication and supercoiling (Hooper, 2001). By stabilizing the DNA-enzyme complex, quinolines prevent the resealing of DNA strands, leading to the inhibition of bacterial replication and ultimately bacterial cell death.

Disruption of Membrane Integrity- Quinoline derivatives also disrupt microbial cell membranes, compromising their integrity and leading to cell lysis. This mechanism is particularly significant in the action of compounds like chloroquine and hydroxychloroquine, which accumulate in the lysosomes and alter the pH balance, disrupting cellular homeostasis and leading to the breakdown of cellular membranes (Savarino et al., 2003). This membrane-disruptive property enhances the permeability of the cell to other antimicrobial agents, facilitating their entry and action.

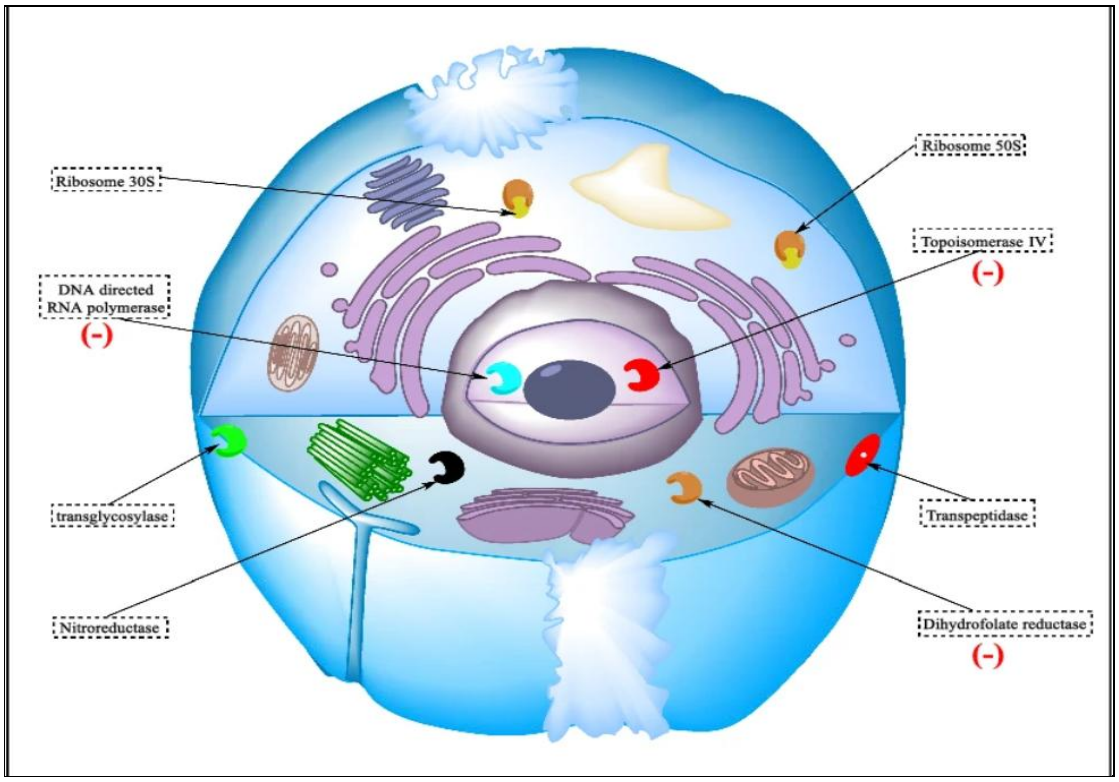


Figure 6: Mechanistic insights and a general representation of proteins involved in replication of various bacteria and the proteins being targeted by quinoline (shown as red "(-)" mark) derivatives. (Source: Kumar, N., Khanna, A., Kaur, K., Kaur, H., Sharma, A., & Bedi, P. M. S. (2023)). Quinoline derivatives volunteering against antimicrobial resistance: rational approaches, design strategies, structure activity relationship and mechanistic insights. *Molecular Diversity*, *27*(4), 1905-1934.)

Interference with Protein Function- Another critical antimicrobial mechanism of quinoline derivatives involves the interference with protein synthesis and function. For instance, mefloquine, primarily used as an antimalarial, inhibits protein synthesis by interfering with the elongation step of translation. This inhibition occurs through binding to ribosomes, preventing the proper alignment of tRNA and mRNA, thereby stalling protein elongation and leading to cellular dysfunction (Tan et al., 2011).

Inhibition of Nucleic Acid Synthesis- Quinoline derivatives also exhibit the ability to inhibit nucleic acid synthesis. This is particularly evident in the action of compounds such as clioquinol, which interferes with both DNA and RNA synthesis. Clioquinol chelates essential metal ions, such as zinc and iron, that are cofactors for various nucleic acid polymerases, thereby inhibiting their activity and leading to a reduction in nucleic acid synthesis (You et al, 2018). This mechanism is crucial in preventing the replication and transcription processes necessary for microbial survival.

Generation of Reactive Oxygen Species (ROS)- The generation of ROS is another significant antimicrobial mechanism associated with quinoline derivatives. ROS are highly reactive molecules that cause oxidative damage to cellular components, including lipids, proteins, and DNA. Quinoline derivatives like quinacrine and quinaldine promote the production of ROS within microbial cells, leading to oxidative stress and cellular damage (Xu et al., 2014). This oxidative damage disrupts essential cellular functions, ultimately resulting in cell death.

CONCLUSION

Quinoline derivatives are an important class of antimicrobial agents known for their broad-spectrum efficacy against a variety of pathogens. The effectiveness of these compounds is rooted in their ability to disrupt critical biological processes within microbial cells. This review integrates the key points from

recent advancements on the antimicrobial mechanisms of quinoline derivatives, the role of Structure-Activity Relationship (SAR) studies in optimizing their effectiveness, research gaps, and future directions.

Antimicrobial Mechanisms of Quinoline Derivatives

Quinoline derivatives employ multiple mechanisms to exert their antimicrobial effects. Quinolones, such as ciprofloxacin and norfloxacin, target bacterial DNA gyrase and topoisomerase IV. These enzymes are essential for DNA replication and supercoiling. By stabilizing the DNA-enzyme complex, quinolines prevent the resealing of DNA strands, halting bacterial replication and leading to cell death (Hooper, 2001). Compounds like chloroquine and hydroxychloroquine disrupt microbial cell membranes by altering the pH balance within lysosomes. This disruption leads to cellular homeostasis breakdown and cell lysis (Savarino et al., 2003). Mefloquine, used primarily as an antimalarial, inhibits protein synthesis by binding to ribosomes and stalling the elongation step of translation (Tan et al., 2011). Clioquinol interferes with DNA and RNA synthesis by chelating essential metal ions, which are cofactors for nucleic acid polymerases, thereby inhibiting their activity (Park et al., 2005). Quinoline derivatives such as quinacrine and quinaldine induce the production of ROS within microbial cells, leading to oxidative stress and cellular damage (Al-Abdullah et al., 2017).

Despite significant progress, several research gaps remain in the development of quinoline derivatives as antimicrobial agents. Understanding the specific mechanisms by which microbes develop resistance to quinoline derivatives is essential. This includes studying mutations in target enzymes and the role of efflux pumps. More research is needed to balance antimicrobial potency with safety. Investigating the pharmacokinetics and pharmacodynamics of new derivatives can help mitigate adverse effects. Developing quinoline derivatives with broad-spectrum activity against both Gram-positive and Gram-negative bacteria remains a challenge. Structural modifications that enhance efficacy across diverse pathogens are needed. Exploring the potential of quinoline derivatives in combination with other antimicrobial agents could lead to synergistic effects and reduce the likelihood of resistance development.

Future Directions: Advancing quinoline derivatives as antimicrobial agents involves several key strategies like innovative SAR approaches, targeted drug delivery, new molecular targets, and clinical trials. Utilizing advanced computational methods and high-throughput screening to identify promising derivatives rapidly. Developing targeted delivery systems that enhance the concentration of quinoline derivatives at the site of infection, thereby increasing efficacy and reducing systemic toxicity. Identifying and validating new molecular targets within microbial cells that quinoline derivatives can exploit. Conducting comprehensive clinical trials to evaluate the safety and efficacy of novel quinoline derivatives in diverse patient populations. The continued development and optimization of quinoline derivatives hold significant promise for combating antimicrobial resistance. By addressing the current research gaps and pursuing innovative approaches, these compounds can be pivotal in developing novel therapies against resistant pathogens, ultimately improving patient outcomes and public health.

REFERENCES

1. Jin, G., Li, Z., Xiao, F., Qi, X., & Sun, X. (2020). Optimization of activity localization of quinoline derivatives: Design, synthesis, and dual evaluation of biological activity for potential antitumor and antibacterial agents. *Bioorganic chemistry*, *99*, 103837.
2. Cebeci, Y. U., & Karaoğlu, Ş. A. (2022). Quinolone-Rhodanine Hybrid Compounds: Synthesis and Biological Evaluation as Anti-Bacterial Agents. *ChemistrySelect*, *7*(22), e202201007.
3. Thakare, P. P., Shinde, A. D., Chavan, A. P., Nyayanit, N. V., Bobade, V. D., & Mhaske, P. C. (2020). Synthesis and Biological Evaluation of New 1, 2, 3-Triazolyl-Pyrazolyl-Quinoline Derivatives as Potential Antimicrobial Agents. *ChemistrySelect*, *5*(15), 4722-4727.
4. Kardile, R. A., Sarkate, A. P., Lokwani, D. K., Tiwari, S. V., Azad, R., & Thopate, S. R. (2023). Design, synthesis, and biological evaluation of novel quinoline derivatives as small molecule mutant EGFR inhibitors targeting resistance in NSCLC: In vitro screening and ADME predictions. *European Journal of Medicinal Chemistry*, *245*, 114889.
5. El-Saghier, A. M., El-Naggar, M., Hussein, A. H. M., El-Adasy, A. B. A., Olish, M., & Abdelmonsef, A. H. (2021). Eco-Friendly Synthesis, Biological Evaluation, and In Silico Molecular Docking Approach of Some New Quinoline Derivatives as Potential Antioxidant and Antibacterial Agents. *Frontiers in Chemistry*, *9*, 679967.
6. Mahamoud, A., Chevalier, J., Davin-Regli, A., & Barbe, J. (2006). Quinoline derivatives as promising inhibitors of antibiotic efflux pump in multidrug resistant Enterobacter aerogenes isolates. *Current drug targets*, *7*(7), 843-847.

7. Kumar, P. (2020). A review on quinoline derivatives as anti-methicillin resistant Staphylococcus aureus (MRSA) agents. *BMC chemistry*, *14*(1), 17.
8. Singh, V. K., Kumari, P., Som, A., Rai, S., Mishra, R., & Singh, R. K. (2023). Design, synthesis and antimicrobial activity of novel quinoline derivatives: an in silico and in vitro study. *Journal of Biomolecular Structure and Dynamics*, 1-21.
9. Teng, P., Li, C., Peng, Z., Marie, V. A., Nimmagadda, A., Su, M., ... & Cai, J. (2018). Facilely accessible quinoline derivatives as potent antibacterial agents. *Bioorganic & medicinal chemistry*, *26*(12), 3573-3579.
10. Dalhoff, A. (2012). Global fluoroquinolone resistance epidemiology and implictions for clinical use. *Interdisciplinary perspectives on infectious diseases*, *2012*(1), 976273.
11. Hooper, D. C. (2000). Mechanisms of action and resistance of older and newer fluoroquinolones. *Clinical infectious diseases*, *31*(Supplement_2), S24-S28.
12. Piddock, L. J. (1999). Mechanisms of fluoroquinolone resistance: an update 1994–1998. *Drugs*, *58*(Suppl 2), 11-18.
13. Van Bambeke, F., Michot, J. M., Van Eldere, J., & Tulkens, P. M. (2005). Quinolones in 2005: an update. *Clinical Microbiology and infection*, *11*(4), 256-280.
14. Ventola, C. L. (2015). The antibiotic resistance crisis: part 1: causes and threats. *Pharmacy and therapeutics*, *40*(4), 277.
15. World Health Organization. (2022). *Global antimicrobial resistance and use surveillance system (GLASS) report 2022*. World Health Organization.
16. Ren, L., Xu, W., Overton, J. L., Yu, S., Chiamvimonvat, N., & Thai, P. N. (2020). Assessment of hydroxychloroquine and chloroquine safety profiles-a systematic review and meta-analysis. *MedRxiv*.
17. Tomé, A. M., & Filipe, A. (2011). Quinolones: review of psychiatric and neurological adverse reactions. *Drug safety*, *34*, 465-488.
18. Ren, L., Xu, W., Overton, J. L., Yu, S., Chiamvimonvat, N., & Thai, P. N. (2020). Assessment of hydroxychloroquine and chloroquine safety profiles-a systematic review and meta-analysis. *MedRxiv*.
19. Kohanski, M. A., Dwyer, D. J., & Collins, J. J. (2010). How antibiotics kill bacteria: from targets to networks. *Nature Reviews Microbiology*, *8*(6), 423-435.
20. Dadgostar, P. (2019). Antimicrobial resistance: implications and costs. *Infection and drug resistance*, 3903-3910.
21. Morrison, L., & Zembower, T. R. (2020). Antimicrobial resistance. *Gastrointestinal Endoscopy Clinics*, *30*(4), 619-635.
22. Marston, H. D., Dixon, D. M., Knisely, J. M., Palmore, T. N., & Fauci, A. S. (2016). Antimicrobial resistance. *Jama*, *316*(11), 1193-1204.
23. Acar, J., & Rostel, B. (2001). Antimicrobial resistance: an overview. *Revue Scientifique et Technique-Office International des Epizooties*, *20*(3), 797-810.
24. Sarro, A. D., & Sarro, G. D. (2001). Adverse reactions to fluoroquinolones. An overview on mechanistic aspects. *Current medicinal chemistry*, *8*(4), 371-384.
25. Alves, C., Mendes, D., & Marques, F. B. (2019). Fluoroquinolones and the risk of tendon injury: a systematic review and meta-analysis. *European journal of clinical pharmacology*, *75*, 1431-1443.
26. Al-Bari, M. A. A. (2015). Chloroquine analogues in drug discovery: new directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases. *Journal of Antimicrobial Chemotherapy*, *70*(6), 1608-1621.
27. Schrezenmeier, E., & Dörner, T. (2020). Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nature Reviews Rheumatology*, *16*(3), 155-166.
28. Ben-Zvi, I., Kivity, S., Langevitz, P., & Shoenfeld, Y. (2012). Hydroxychloroquine: from malaria to autoimmunity. *Clinical reviews in allergy & immunology*, *42*, 145-153.
29. Kappe, C. O. (2004). Controlled microwave heating in modern organic synthesis. *Angewandte Chemie International Edition*, *43*(46), 6250-6284.
30. Taylor, R. J., & Katritzky, A. R. (2005). *Comprehensive organic functional group transformations II*. Elsevier.
31. Patel, B. K., Dahiya, A., Sahoo, A. K., Chakraborty, N., & Das, B., (2022). Updates on hypervalent-iodine reagents: metal-free functionalisation of alkenes, alkynes and heterocycles. *Organic & Biomolecular Chemistry*, *20*(10), 2005-2027.
32. Plutschack, M. B., Pieber, B., Gilmore, K., & Seeberger, P. H. (2017). The hitchhiker's guide to flow chemistry‖. *Chemical reviews*, *117*(18), 11796-11893.
33. Seyden-Penne, J. (1997). *Reductions by the alumino-and borohydrides in organic synthesis*. John Wiley & Sons.
34. Mittal, R. K., Aggarwal, M., Khatana, K., & Purohit, P. (2023). Quinoline: Synthesis to application. *Medicinal Chemistry*, *19*(1), 31-46.
35. Tanaka, K. (2009). *Solvent-free organic synthesis*. John Wiley & Sons.
36. Welton, T. (2004). Ionic liquids in catalysis. *Coordination chemistry reviews*, *248*(21-24), 2459-2477.
37. Tombesi, A., & Pettinari, C. (2021). Metal organic frameworks as heterogeneous catalysts in olefin epoxidation and carbon dioxide cycloaddition. *Inorganics*, *9*(11), 81.
38. Furukawa, H., Cordova, K. E., O'Keeffe, M., & Yaghi, O. M. (2013). The chemistry and applications of metal-organic frameworks. *Science*, *341*(6149), 1230444.
39. Janiak, C., & Vieth, J. K. (2010). MOFs, MILs and more: concepts, properties and applications for porous coordination networks (PCNs). *New Journal of Chemistry*, *34*(11), 2366-2388.
40. Huang, N. Y., Zheng, Y. T., Chen, D., Chen, Z. Y., Huang, C. Z., & Xu, Q. (2023). Reticular framework materials for photocatalytic organic reactions. *Chemical Society Reviews*.