wjpmr, 2023, 9(4), 60-64

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Review Article

ISSN 2455-3301

WJPMR

A COMPREHENSIVE REVIEW ON ANTIBACTERIAL COMPOUNDS

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Article Received on 07/02/2023 **Article Revised on 27/02/2023** **Article Accepted on 19/03/2023**

ABSTRACT

Quinolones are synthetic, broad-spectrum antibacterial drugs that were initially developed during the manufacturing of chloroquine. In 1962, the first quinolone, nalidixic acid, became therapeutically available. It was largely used to treat urinary tract infections caused by Gram-negative bacteria like Escherichia coli and other potentially harmful strains. The development of novel quinolone analogues with better activity that could be utilised to treat different bacterial infections has recently been the subject of extensive investigation. Site-specific substitution is used to produce these novel analogues, and the modifications at the C-6 and C-8 locations lead to more potent drugs. Fluroquinolones, which account for a sizeable portion of quinolones used in medicine, are produced by substituting a fluorine atom at the C-6 position. By swapping the rings of the piperazine or methyl piperazine, pyrrolidinyl, or piperidinyl compounds, effective analogues can also be made. Nine analogues in total are listed in this review. This is due to a number of factors, some of which are discussed in this article, but there is also a lot of ongoing research being done to find new, powerful antimicrobials. There are numerous causes for this, some of which are covered in this article, but there is also a tonne of active research being done to find new, effective antimicrobials.

KEYWORDS: piperazine or methyl piperazine, pyrrolidinyl, or piperidinyl compounds.

INTRODUCTION

Early in the 20th century, infectious diseases—of which bacterial infections accounted up by nearly one-third—were the most prevalent cause of human illness and death.[1] With over 220 million cases and over 3 million fatalities yearly, malaria also has a significant impact on worldwide human health in addition to bacterial infections.[2] While several medicines were employed to treat these conditions, the development of antibiotic drugs opened up new therapy options for bacterial infections. One of the big scientific turning points was Alexander Fleming's 1928 discovery of penicillin and the subsequent development of synthetic antibiotics like quinolones.[3,4] However, as antibiotic discovery has advanced, antibiotic-resistant bacteria have become more prevalent and are now a rare health concern.[5] Here, we concentrate on quinolones, a significant class of synthetic antibiotics that are biologically active and broad-spectrum antibacterial medications.[6] It can be found in many naturally occurring biologically active compounds. Quinolones have received a lot of attention in the fields of medical and synthetic chemistry due to their beneficial therapeutic properties.[9] Nalidixic acid was first utilized in clinical settings to treat urinary tract infections brought on by enteric bacteria in the latter 1960s. Oxalinic acid was the most notable of several new generations of quinolones that were produced and became accessible for clinical usage around the 1970s.[10–12] Quinolones were an underutilized class of antibacterial drugs up until 1980, and a second generation of quinolones was later created. In the search for powerful quinolones, it was found that changing the groups at positions C-6 and C-8 results in more potent antibacterial analogs.[13] The replacement of fluorine at C-6 and a key ring substituent piperazine or methyl piperazine, pyrrolidinyl, and piperidinyl are the two alterations to the quinolones' basic skeleton that have the greatest impact. Due to the insertion of fluorine at C-6, most clinically used quinolones are fluoroquinolones (FQ).[14–16] Broad-spectrum antibiotics that are effective against both Gram-positive and Gram-negative bacteria are known as fluoroquinolones (formerly known as simply quinolones)**figure1**. In addition to their broad-spectrum activity, fluoroquinolones have other qualities that contribute to their success, including strong oral bioavailability following delivery, minimal toxicity, and acceptable pharmacokinetics.[17] Fluoroquinolones are still among the most effective antibacterial medicines, despite the fact that they can cause unwanted side effects. Significant effort has been put into the structural evolution of fluoroquinolones in order to create novel analogs with increased efficacy. Fluoroquinolones have primarily been used to treat gastrointestinal and stomach

infections, skin and soft tissue infections, respiratory tract infections, sexually transmitted illnesses, urinary tract infections (UTI), and infections of the bones and joints.[11,18] Fluoroquinolone with broad-spectrum activity have also been widely used in veterinary medicine to treat bacterial infections in pets, aquaculture, and food-producing animals. Although there are several fluoroquinolones on the market, how well these antibacterials are used relies much on the types of animals and where they are found.[18] They are useful in treating and preventing respiratory, gastrointestinal, and complicated urinary tract infections in domestic animals, fish, poultry, and other livestock.[19] Some quinolones, such as 6-chloro-7-methoxy-4(1H)-quinolones, are effective against many stages of Plasmodium infection and have good antimalarial properties.[2] With the substitution of various benzenoid ring components and aryl moieties, the (1H)-quinolone's and its tetrahydro acridine analogue's antimalarial activity was also demonstrated.[20]

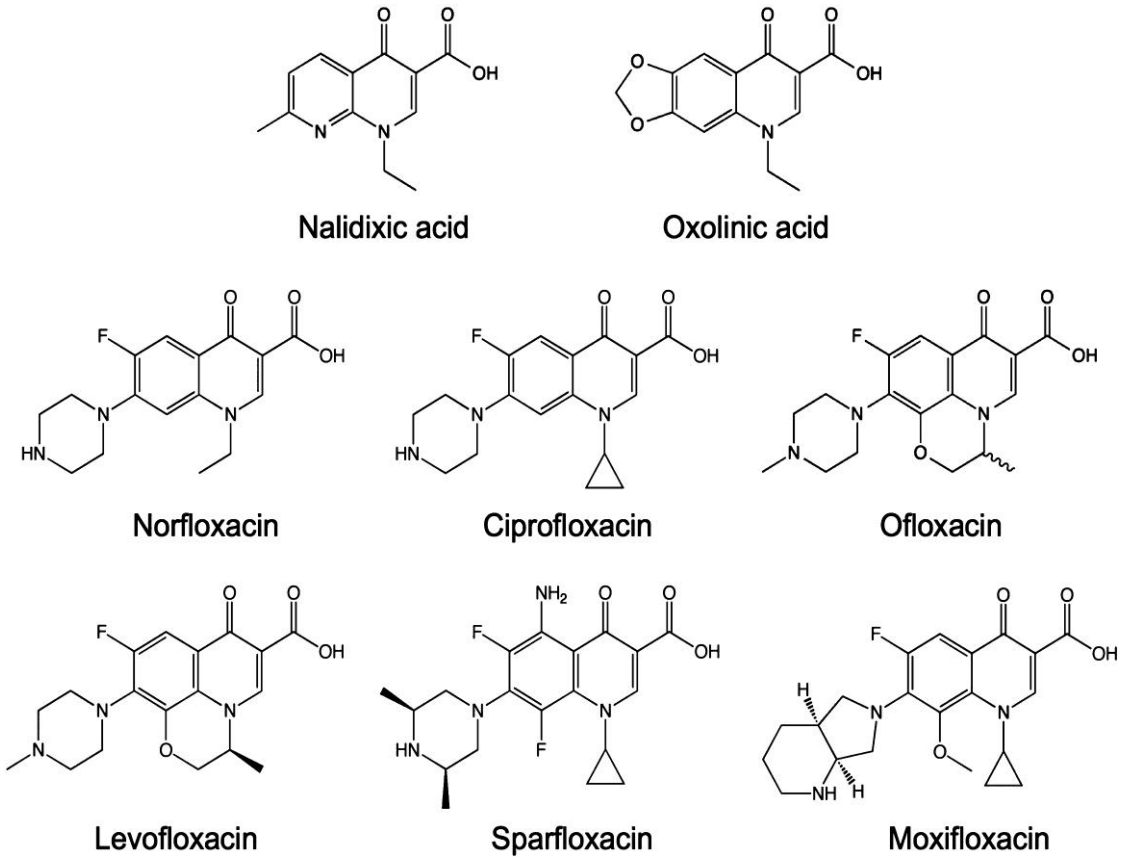

Figure 1: Various quinolones used in different diseases for their antimicrobial activity.

Significance of aryl quinolones in medicine

Due to its broadened antibacterial spectrum and advantageous pharmacokinetics, quinolone analogs are widely employed in clinical settings around the globe, however, research into novel hybrid next-generation quinolones is still ongoing. Gatifloxacin, levofloxacin, and ciprofloxacin are three of the most effective quinolone options that are frequently prescribed. There are some quinolones, such as halogenated quinolones, that are more harmful to patients than beneficial, although these toxic counterparts should be administered when there is no other choice and the toxic damage is little compared to the pathogen harm.[21] Infections of the lungs, such as cystic fibrosis, can also be treated with quinolones. Although cytotoxic, clinafloxacin can be used to treat multidrug-resistant bacteria. Aspergillus cepacia.[21] Anionic fluoroquinolones are also the most effective treatment for respiratory illnesses caused by Pseudomonas aeruginosa. Most antibiotics have trouble penetrating and inhibiting bacterial growth in P. aeruginosa-based disorders like cystic fibrosis because the bacteria build up a thick biofilm of anionic polymers including rhamnolipids and alginate.However, due to their negatively charged composition, fluoroquinolones have the capacity to traverse mucus and so have higher pharmacodynamics.[22] The Federal Drug Administration (FDA) has also authorized the use of some quinolones, including ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, and gatifloxacin, in children for a variety of ailments, including conjunctivitis, otitis, sinusitis, respiratory tract infections, pneumonia, UTI, and gastrointestinal conditions.[23] Fluoroquinolones can be used to treat tuberculosis (TB), as opposed to other active medicines, which typically take six months or longer to work.[24] Since Mycobacterium tuberculosis strains are so resistant to antibiotics, the emergence of multi-drug resistance in these strains has already frightened the medical world. Quinolones experience the

same destiny as antibiotics because many M. tuberculosis strains cause mutations in the GyrA and GyrB genes that code for the DNA gyrase enzyme.[25–27] Numerous M. tuberculosis strains developed high levels of levofloxacin resistance as a result of mutations in the amino acids Ala90 and Asp94 of GyrA.[28]

Mode of action of Aryl quinolones

The principal target of quinolones has been known to be the bacterial enzyme gyrase since 1977. Later, it was proposed that this enzyme might possibly be a target of quinolones in light of the discovery of topoisomerases. Analysis of Escherichia coli strains carrying drug-resistance mutations in these enzymes showed that quinolones inhibit gyrase and topoisomerase-IV as primary and secondary targets, respectively.[28] A number of high-resolution structures of topoisomerase with DNA in various catalytic states have demonstrated how topoisomerases alter the topology of DNA.[23-25] According to a recent study, various sorts of interactions mediate the interaction between quinolones and human and bacterial type II topoisomerase. The gyrase and topoisomerase-IV enzymes are the targets of the quinolones, which have been demonstrated to stop bacterial growth.[29] The cell genome, which is necessary for cell survival and reproduction, may be damaged by these enzymes. Quinolones reduce the amount of enzyme-DNA cleavage complexes, which prevents cells from growing and dividing.[30,31] Due to their ability to turn gyrase and topoisomerase IV into cellular toxins, quinolones are known as topoisomerase poisons.

New antimicrobial targets

Numerous important genes that may be the targets of antimicrobial drugs have been found thanks to the whole-genome sequencing of many pathogenic bacteria. Additionally, pre-clinical research has thus far indicated that the compound has significant toxicity for mammalian cells.[35] PDF-713 is a peptide deformylase (PDF) inhibitor with broad-spectrum action against Haemophilus influenzae and Gram-positive bacteria.[36] A crucial stage in bacterial cell protein synthesis, but not in that of eukaryotic cells, the formylation and subsequent deformylation of the methionine residue that starts protein synthesis makes it an appealing antibacterial target. The bacterial deformylase's three-dimensional crystal structure is available, which has facilitated the production of potential chemicals that function as inhibitors. It has been determined that the new class of N-alkyl urea hydroxamic acids known as PDF-713 is an inhibitor of PDF. It was thought that these chemicals would exhibit selective antibacterial activity and that the evolution of resistance would not be a frequent occurrence since they target a particular bacterial enzyme that is necessary to allow efficient protein synthesis in the majority of bacterial species. While S. aureus and H. influenza have shown to rapidly develop resistance to the chemical in vivo, limiting its use as a broad-spectrum drug, this appears to be true for Streptococcus pneumoniae and H. influenza. The lipopolysaccharide production in Gram-negative bacteria is inhibited by ACHN-971. It is still in the early stages of pre-clinical development by Achaogen and exhibits good in vitro performance against P. aeruginosa and other Gram-negative bacteria. Finally, riboswitches are a fascinating new class of targets that BRX-1555 inhibits.[37] By controlling, riboswitches manage molecular biosynthesis. Synthesis of mRNA. To date, numerous unique types of highly conserved riboswitches have been discovered. They are present in both Gram-positive and Gram-negative bacteria, as well as more than 100 different bacterial and fungal species, many of which are diseases for humans. In fact, riboswitches have been found in more than 2000 different instances.[37,38] Riboswitch inhibitors can also be found in nature. To illustrate the potential of riboswitches as antibacterial targets, consider how thiamine pyrophosphate riboswitches control thiamine biosynthesis by stopping transcription in response to growing thiamine pyrophosphate concentrations.[39] One of the earliest inhibitors created was BRX-1555. It shows interesting in vitro efficacy against C. difficile and targets the riboswitches in that pathogen.

CONCLUSION

There is considerable doubt that during the past ten years, the clinical use of new potent antimicrobial agents has not been able to keep up with the need for new antimicrobial agents due to the persistent development of resistance among significant human bacterial diseases. Quinolones are used as broad-spectrum antibacterial medicines that work against both Gram-positive and Gram-negative bacteria all over the world. Numerous quinolone compounds have antiviral, antimalarial, and anticancer properties. Quinolones developed into a distinct class of synthetic pharmaceuticals after being initially created as a result of chloroquine manufacturing. Different synthetic techniques are now being investigated to create novel quinolone analogs that are more potent. Some bacteria develop resistance to them as a result of the abuse of these medications, and these bacterial strains are now a common threat globally.

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