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Quinolones: Understanding the Drug Designing to Combat Drug Resistance

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Short Communication

Incidences of drug resistances have increased in the recent past and with the ongoing discoveries of new infectious diseases, medicine practice in management of infections and treatment of ailments have become a challenging situation in the medical care settings. Therefore, there is an urgent demand for a new class of antimicrobial agent with a different mode of action and it led medicinal chemists to explore a wide variety of chemical structures. In pursuit of this goal, research efforts have been directed towards the discovery of new chemical entities that are effective antimicrobial agents. The discovery and development of antimicrobial agents that has met with enormous success over the past few years provided many classes of natural products and semi-synthetic or synthetic compounds. Nitrogen containing heterocyclic compounds is well studied for their broad spectrum of activities. Among them quinolones and their derivatives constitute a crucial class of organic compounds which have been reported to posses versatile activities. The quinolones are a family of synthetic broad-spectrum antibiotic drugs [1-3]. Quinolones and their derivatives occur in numerous natural products, many of which possess interesting physiological and biological properties [1].

Isolated as a by-product of the synthesis of chloroquinine, nalidixic acid was the first therapeutically potential quinolone moiety and used for the treatment of urinary tract infections for many years. Ciprofloxacin, moxifloxacin, and gatifloxacin are some fluorinated-quinolones (FQ) which have broad spectrum antimicrobial activity for the cure of diverse pathogenic diseases. Side effects are relatively few with the use of these fluoroquinolones (FQs). Microbial resistance may be developed. In some cases rare and potentially fatal side effects were also reported and few drugs such as clinafloxacin, grepafloxacin, trovafloxacin, and temafloxacin were withdrawn from the market due to severe toxic side effects [1-3].

The FQs are potent bactericidal agents against *E. coli* and various species of Salmonella, Shigella, Enterobacter, Campylobacter, and Neisseria, *P. aeruginosa*, staphylococci, but not against methicillin-resistant strains. Activity against streptococci is limited to a subset of the quinolones, including le ofloxacin, moxifloxacin and gatifloxacin [4]. Several intracellular bacteria are inhibited by FQs which include species of Chlamydia, Mycoplasma, Legionella, Brucella, and Mycobacterium [5,6]. Several of FQs have activity against anaerobic bacteria, like garenoxacin and gemifloxacin [7].

The quinolone antibiotics target bacterial DNA gyrase and topoisomerase IV [8]. For many gram-positive bacteria (such as *S. aureus*), topoisomerase IV is the primary activity inhibited by the FQs. In contrast, for many gram-negative bacteria (such as *E. coli*), DNA gyrase is the primary quinolone target [9]. The drugs inhibit gyrase-mediated DNA super coiling at concentrations that correlate well with those required to inhibit bacterial growth. Mutations of the gene that encodes the A subunit polypeptide can confer resistance to these drugs [8]. This enzyme is the target for some anti-neoplastic agents. Quinolones inhibit eukaryotic type II topoisomerase only at much higher concentrations (100 mg/ml to 1000 mg/ml) [10].

Resistance to quinolones may develop during therapy via mutations in the bacterial chromosomal genes encoding DNA gyrase or topoisomerase IV or by active transport of the drug out of the bacteria [11]. Resistance has increased after the introduction of FQs, especially in *Pseudomonas* and *staphylococci* [12]. Increasing FQ resistance also is being observed in *C. jejuni*, *Salmonell*a, *N. gonorrhoeae*, and *S.pneumonia* [13].

FQs and various quinolone derivatives are used in treatment of various urinary tract infection; prostatitis, sexually transmitted diseases; gastrointestinal and abdominal infections; respiratory tract infections; bone, joint, and soft tissue infections, etc [14-17].

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