Chapter (1) Introduction

1.1. General introduction

Antibiotic is a substance or compound that kills bacteria or inhibits their growth. Antibiotics belong to the broader group of antimicrobial compound, used to treat infections caused by microorganisms, including fungi and protozoa[(1)].

Given in high therapeutic doses, the aminoglycosides, cephalosporins penicillins and polymyxins antibiotics are generally considered bactericidal whereas chloramphenicol, erythromycin, sulphonamides and tetracyclines are usually bacteriostatic. However, an antibiotic which is bactericidal in a certain concentration may become bacteriostatic at lower concentration [(2)].

Since the development of newer quinolones and their release [(3)] in the mid 1980's, they have been approved and used extensively for the treatment of a broad range of infections, including urinary tract infections of a wide variety of types, as well as bacterial infections of the gastrointestinal tract [(4)]. In addition, they are effective for the treatment of certain type of sexually transmitted diseases [(5)] and for selected infections of the respiratory tract [(6)] skin, and soft tissues [(7)]. Because of their ability to penetrate into prostatic tissue, prostatic fluid and their wide spectral of activity, these antimicrobial agents are ideal in the treatment of bacterial prostatitis.

1.1.1. Fluoroquinolones

The quinolone carboxylic acids or 4-quinolones are a group of synthetic antibacterial agents. The term 4-quinolone has been used as a generic name for the common 4-oxo-l, 4-dihydroquinoline skeleton [(8)]. Under this system,

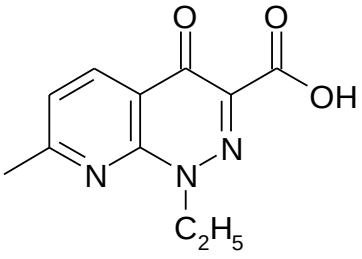
nalidixic acid, a naphthyridene derivative is an 8-aza-4-quinolone which was originally isolated as a by-product by Lesher and associates from a distillate during chloroquine synthesis in antimalarial research [(8)]. Modifications of the structure of nalidixic acid has produced related antibacterial agents such as oxolinic acid (OXO), piromidic acid (PIR), and cinoxacin (CIN), although some of these have a greater activity in vitro against some Gram-negative and Gram-positive organisms, cinoxacin is restricted mainly to the treatment of urinary tract infections and is bactericidal [(9)]. This agent appears to be also effective in the prophylaxis of recurrent lower urinary tract infections. None has been considered to represent a significant clinical advance over the parent nalidixic acid (NAL), However chemical modifications of the basic quinolones molecules have resulted in a host of new compounds which markedly improved biological and toxicological properties.

Flumequine (FLU) was the first fluorinated quinolones to be synthesised. Addition of a piperazine radical at position 7 as in pipemidic acid (PIP) appears to confer some activity against pseudomonas [(10)]. Modification of nalidixic acid by the introduction of 6-fluoro and 7-(1-piperazinyl) substituents gave rise to a third generation named fluoroquinolones, with a broader spectrum of activity than nalidixic acid and pharmacokinetic properties more suitable for the treatment of systemic infections. They include pipemidic acid (PIP), norfloxacin (NOR), ciprofloxacin (CIP), ofloxacin (OFL), lomefloxacin HCL (LOM), pefloxacin (PEF), and enoxacin (ENO). Following the discovery of nalidixic acid in 1962, numerous structural modifications have been made in the quinoline nucleus to increase antimicrobial activity and improve pharmacokinetic performance [(11)]. A major advance occurred during the 1980s with the discovery that a fluorine atom at position 6 conferred broad and potent antimicrobial activity, e.g. norfloxacin, but still with relatively less activity for gram-positive and anaerobic organisms than gram-negative bacteria.

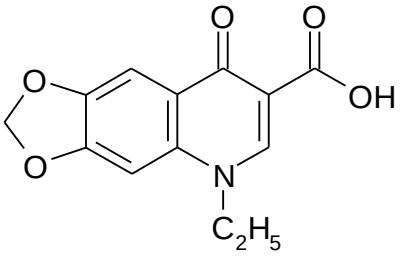
Subsequent developments produced quinolones with further improvements, predominantly in solubility (e.g. ofloxacin), antimicrobial activity (e.g. ciprofloxacin) or prolonged serum half life (e.g. pefloxacin). Recent modifications have attempted to achieve an optimal blend of favorable properties together with potential for undesirable side effects [(12)].

1.1.1.1. Chemical structure of flouroquinolines

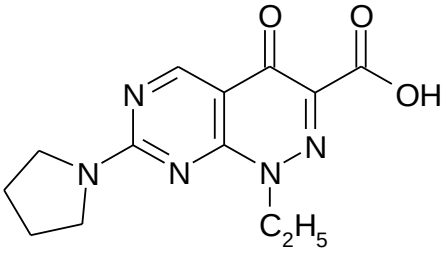
Antimicrobial quinolones contain one acidic and one basic functional group and at physiological pH they exist as mixture of the neutral and zwitterionic forms [(13)]. The ratio of the neutral to zwitterionic species for a given compound is important because it determines the distribution properties of the drug in vivo. The apparent pKa value associated with carboxylic acid function was influenced by the number of fluorines in the molecule, while the pKa value associated with the piperazinyl nitrogen was influenced mainly by the presence of N-methyl substituent [(13)] as shown in Figure (1).



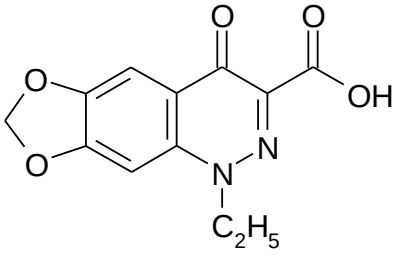
Nalidixic acid (NAL)



Oxolinic acid (OXO)



Piromidic acid (PIR)



Cinoxacin (CIN)

Figure (1). General structure of Fluoroquinolones