

## **Inhibitors of Nucleic Acid Synthesis**

The antibacterial drugs that inhibit nucleic acid synthesis function by inhibiting (1) DNA polymerase and DNA helicase or (2) RNA polymerase to block replication or transcription, respectively. These drugs are not as selectively toxic as other antibiotics because bacteria and eukaryotes do not differ greatly with respect to nucleic acid synthesis. The antibacterial agents that act as inhibitors of nucleic acid synthesis do so in one of three main ways as shown in Figure (1).

### **Inhibitors of synthesis of precursors**

Sulfonamides

Trimethoprim

### **Inhibitors of DNA replication**

Quinolones

### **Inhibitors of RNA polymerase**

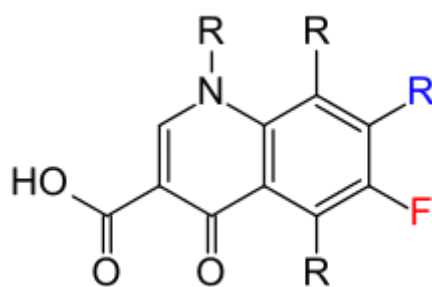
Rifampicin

Figure (1):Inhibitors of nucleic acid synthesis

These compounds include antibacterial quinolones, novobiocin and rifampicin. Sulfonamides, 5-nitroimidazole and (probably) nitrofurans also affect DNA synthesis and will be considered under this heading .

## **Quinolones**

Quinolones form a large family of synthetic ,broad spectrum, bactericidal antibacterial agents. The first generation of quinolones began with the introduction of nalidixic acid in 1962 for treatment of urinary tract infections in humans. They exert their antibacterial effect by preventing bacterial DNA from unwinding and duplicating .



Structure of quinolone

### Quinolones can be classified into two subclass:

#### Quinolones

1st Generation – Narrow  
Spectrum

Nalidixic acid, Cinoxacin

#### Fluoroquinolones

Ciprofloxacin  
Enoxacin  
Garenoxacin  
Levofloxacin  
Lomefloxacin  
Norfloxacin  
Ofloxacin  
Sparfloxacin  
Gatifloxacin  
Moxifloxacin  
Trovaflaxacin

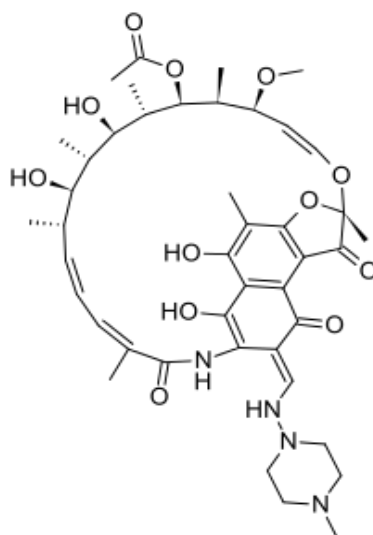
### Mode of action

Quinolones are small and hydrophilic molecules that diffuse easily through the peptidoglycan and the cytoplasmic membrane and rapidly reach their target. The main quinolone target is one of topoisomerase, the DNA gyrase (is a tetramer composed of two pairs of  $\alpha$  and  $\beta$  subunits, and the primary target of the action of nalidixic acid and other quinolones is the  $\alpha$  subunit of DNA gyrase) which is responsible for cutting one of the chromosomal DNA strands at the beginning of the supercoiling process. The nick is only introduced temporarily and later the two ends

are joined back together (i.e., repaired). The quinolone molecule forms a stable complex with DNA gyrase thereby inhibiting its activity and preventing the repair of DNA cuts.

## Rifampicin

Rifampicin or rifampin is the most important member of rifamycin family in clinical use. Rifampicin was introduced in 1967 for treatment of tuberculosis and inactive meningitis, along with pyrazinamide, isoniazid, ethambutol, and streptomycin. Rifampicin is a bactericidal drug inhibits bacterial DNA-dependent RNA synthesis by inhibiting bacterial DNA-dependent RNA polymerase.



Structure of rifampicin

## Mode of action

Rifampicin inhibits RNA synthesis by inhibiting bacterial DNA-dependent RNA polymerase (RNA polymerase consists of a core enzyme made up of four polypeptide subunits, and rifampicin specifically binds to the  $\beta$  subunit). Rifampicin binds to RNA polymerase at a site adjacent to the RNA polymerase active center and blocks RNA synthesis by preventing extension of RNA products beyond a length of 2-3 nucleotides.