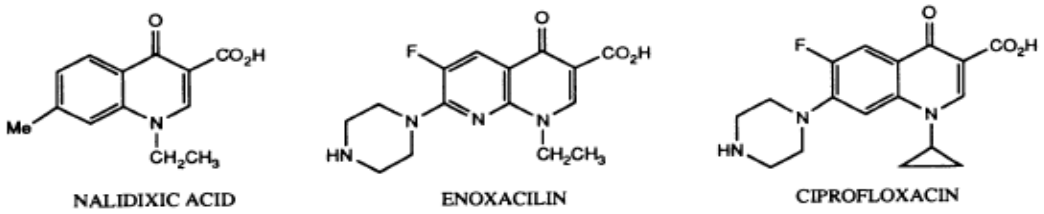
Agents which act on nucleic acid transcription and replication

Quinolones and fluoroquinolones

The quinolone and fluoroquinolone antibacterial agents are relatively late arrivals on the antibacterial scene, but are proving to be very useful therapeutic agents. They are particularly useful in **the treatment of urinary tract infections** and also for the treatment of infections which prove resistant to the more established antibacterial agents. In the latter case, microorganisms which have gained resistance to penicillin may have done so by mutations affecting cell wall biosynthesis. Since the quinolones and fluoroquinolones act by a different mechanism, such **mutations** provide no protection against these agents.



Quinolones and fluoroquinolones.

Nalidixic acid was the first therapeutically useful agent in this class of compounds. It is active against Gram-negative bacteria and is useful in the short-term therapy of urinary tract infections. It can be taken **orally**, but unfortunately, bacteria can rapidly develop resistance to it.

Further adjustments led to **ciprofloxacin**, now the agent of choice in treating travellers' **diarrhoea**. It has been used in the treatment of a large range of infections involving the urinary, respiratory, and gastrointestinal tracts as well as infections of skin, bone, and joints. It has been claimed that ciprofloxacin may be the most active broad-spectrum antibacterial agent on the market. Furthermore, bacteria are slow in acquiring resistance to ciprofloxacin, in contrast to nalidixic acid.

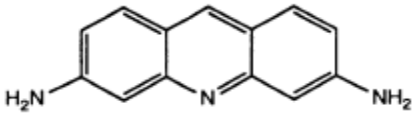
The quinolones and fluoroquinolones are thought **to act on the bacterial enzyme deoxyribonucleic acid gyrase (DNA gyrase)**. *This enzyme*

catalysis the supercoiling of chromosomal DNA into its tertiary structure. A consequence of this is that replication and transcription are inhibited and the bacterial cell's genetic code remains unread. At present, the mechanism by which these agents inhibit DNA gyrase is unclear.

Aminoacridines

Aminoacridines such as **proflavine** are topical antibacterial agents which were used in the Second World War for the treatment of surface wounds.

Proflavine.



Resistance of nucleic acid synthesis antibiotics

Antibiotics considered here can be divided into two mechanisms of action: those which **(1)inhibit nucleotide metabolism** and those which **(2)inhibit enzymes involved in nucleic acid synthesis**.

Sulphonamides

Two mechanisms of chromosomal resistance have been identified. A mutation of **dihydropteroate synthetase (DHPS)** in *Strp. pneumoniae* produces an altered enzyme with reduced affinity for sulphonamides. **Hyperproduction of *p*-amino benzoic acid (PABA)** overcomes the block imposed by inhibition of DHPS. The specific cause of PABA hyperproduction is unknown, though chromosomal mutation is the probable cause.

Duplication of DHPS, with the second version of the enzyme being resistant to the sulphonamides, is the cause of plasmid-acquired resistance. **Two different enzymes have been identified, both with lowered affinity for the antibiotic.**

Trimethoprim

Chromosomal mutations in *E. coli* result in overproduction of **dihydrofolate reductase (DHFR)**. Higher concentrations of trimethoprim, which may not be therapeutically achievable, are therefore required to **inhibit nucleotide metabolism**. Other mutations lower the affinity of DHFR for trimethoprim. These two mechanisms of resistance may coexist in a single strain, effectively increasing the level of resistance to the antibiotic.

Quinolones

The quinolones exert their action by binding to **DNA gyrase (bacterial topoisomerase II)** and inhibiting its functions. Acquired resistance to the quinolones arises due to chromosomal mutations in the genes coding for DNA gyrase. Levels of resistance can be increased by the presence of multiple mutations with a region of the *gyr*A gene known as the quinolone resistance determining region. The exact mechanism of resistance is unknown but is thought to involve a subtle conformational change in DNA gyrase which reduces binding of quinolones.

Other chromosomal mutations resulting in quinolone resistance have been found to **decrease permeability** of the antimicrobial agent.

Rifampicin

Resistance to rifampicin is primarily due to chromosomal mutations resulting in an **altered RNA polymerase** which is less well inhibited by the drug. The mutations tend to be clustered within short conserved regions of the β subunit gene of RNA polymerase.