23.5.1.1 Rifamycins

Rifamycins consist of an aromatic naphthyl core and a polyketide-derived ansa-bridge. Rifamycin was isolated in a strain of *Streptomyces*, now reclassified as *Nocardia mediterranei* (1957). Rifampicin (Figure 23.5) was obtained by chemical modification of rifamycin B. Later, rifaximin was introduced (2004) whose spectrum is similar to that of rifampicin. They are very active against $Gram^+$ bacteria and some $Gram^-$ bacteria. Rifampicin gives a better, more regular absorption and is an excellent drug for tuberculosis and leprosy. Rifaximin is used for gastrointestinal infections.

23.5.1.2 Macrolactones

Macrolactone antibiotics have unsaturated lactone cores with deoxysugars and aromatic motifs. Fidaxomicin is an 18-membered polyketide macrolactone (Figure 23.5), discovered in 1975 from *Actinoplanes deccanensis*. It is bactericidal against $Gram^+$ (aerobic/anaerobic) bacteria but lacks activity against $Gram^-$ bacteria. Fidaxomicin was approved by the FDA (in 2011) for *C. difficile* infections. Narrow spectrum and poor absorption of fidaxomicin in the gastrointestinal tract has proved beneficial for this particular treatment.

23.5.2 Antibiotics Inhibiting DNA Gyrase

A molecule of DNA consists of two linear strands intertwined to form a double helix. In many bacteria, this double-stranded molecule closes into a covalent circle, while in others it is linear. When fully extended, a chromosome is 1000 times as long as the dimensions of the cell. Supercoiling is essential for packing the molecule inside the cell, while unwinding is necessary during replication and transcription.

Topoisomerases are enzymes that convert DNA from one topological form to another, that is, they promote or reverse supercoiling. Topoisomerase I cuts a single strand of the double helix, topoisomerase II cuts both simultaneously.

DNA gyrase is a topoisomerase II which is able to supercoil a relaxed DNA ring (reaction A) at the expense of ATP hydrolysis. While all topoisomerases can relax supercoiled DNA, negative supercoiling is unique to DNA gyrase. It is a validated target, essential in bacteria and absent in humans. DNA gyrase and its close relative topoisomerase IV (which plays an important role in partitioning DNA during cell division) have two subunits, A and B. In gyrase, the subunits are called GyrA and GyrB, respectively. The GyrA subunit is involved in interactions with DNA as it contains the active-site tyrosine responsible for DNA cleavage, while GyrB contains the ATPase active site. Two antibiotic classes, natural Coumarins and synthetic Quinolones, target DNA gyrase using different mechanisms (Table 23.2).

23.5.2.1 Coumarins

Novobiocin (1955) (Figure 23.5) is a coumarin derivative produced by *Streptomyces niveus* and *Streptomyces spheroides*. It is active against $Gram^+$ bacteria and *Haemophilus influenzae* and *Neisseria*. It was used in the treatment of infections caused by resistant staphylococci, but due to toxicity and solubility issues, it was replaced by other products.

23.5.2.2 Quinolones

The quinolone core typically has a N-linked cyclic moiety with various substituents at the C6 and/or C7 positions. The first member, Nalidixic acid (1962), is a by-product of chloroquine (an antimalarial drug) synthesis. Its original trade name Negram® indicates that it is active against $Gram^-$ bacteria. The first-generation quinolones, including oxolinic acid (1967), had weak activity. The synthesis of fluoroquinolones triggered multiple generations of modifications and optimizations for improving potency, spectrum of activity, and countering bacterial resistance. Examples include Ciprofloxacin (Figure 23.5), levofloxacin, and more recent, prulifloxacin.