Many derivatives of chloramphenicol were prepared but only the sulfomethyl analog, thiamphenicol, is in clinical use. It is generally less active than chloramphenicol. The glycinate ester is used as a prodrug for injections. Chloramphenicol has moderate activity against Gram$^+$ and Gram$^-$ bacteria. It is not ideal for the treatment of these infections because of serious toxic reactions in the blood (aplastic anemia, thrombocytopenia). It is still used in the treatment of typhus and meningitis caused by *H. influenzae*.

23.7.2.2 Macrolides

The macrolide antibiotics have in common (1) a large lactone ring (hence the name macrolide), (2) a glycosidically linked aminosugar (sometimes two), and (3) usually a desoxysugar. The lactone ring may contain 12 (macrolides not used in medicine), 14 (erythromycin, oleandomycin), or 16 atoms (leucomycin, spiramycin, tylosin).

Erythromycin is the first clinically useful macrolide (1952; *Streptomyces erythreus*) (Figure 23.7). The structure was determined chemically (1954–1957); the stereochemistry and conformation by X-ray diffraction and NMR. Erythromycin is inactivated by acid. It is very active against Gram$^+$ bacteria.

Oleandomycin (1955; *Streptomyces antibioticus*) is usually administered as a triacetyl derivative which gives higher blood levels. Oleandomycin has a similar spectrum as erythromycin but the MIC is generally higher.

Semisynthetic macrolides include clarithromycin, roxithromycin, and azithromycin, whose spectra are comparable to those of erythromycin.

Telithromycin (1997), the first ketolide (semisynthetic derivative of erythromycin) approved by the FDA, had some rare but serious side effects and was partially withdrawn. Ketolides are effective against strains resistant to older macrolides. Ketolides currently under clinical trials are cethromycin and solithromycin, with better activity against some pathogens.

23.7.2.3 Lincosamides

Lincomycin (1962, *Streptomyces lincolnensis*) has a basic group in the proline part of the molecule and the sugar moiety contains a methylmercapto group (Figure 23.7). Replacement of a hydroxy group by chlorine, with inversion of configuration, resulted in Clindamycin (1967), with improved absorption and higher serum levels. Both are active against Gram$^+$ bacteria, with a spectrum similar to erythromycin. Clindamycin is used in the treatment of infections caused by anaerobic bacteria.

23.7.2.4 Fusidic Acid

Fusidic acid (1962, *Fusidium coccineum*) has a unique steroid-type (fusidane) structure (Figure 23.7) similar to cephalosporin P1. It is active against Gram$^+$ bacteria and Gram$^-$ cocci. Fusidic acid has been in clinical use outside the United States (since 1962) for skin infections. Safety concerns are related to gastrointestinal, allergic, hematological, and neurological adverse effects. Rapid emergence of resistant strains also limits its use. Currently, Cempra (Chapel Hill, U.S.) is evaluating a new dosage regimen in two phase II clinical trials.

23.7.2.5 Streptogramins

The streptogramin family (1950s; various *Streptomyces*) consists of two subgroups, type A and B, simultaneously produced in ~70:30 ratio. Group A streptogramins are cyclic polyunsaturated macrolactones that comprise a hybrid peptide/polyketide structure (e.g., pristinamycin II_A). Group B are cyclic hepta- or hexa-depsipeptides (e.g., quinupristin).

Streptogramins have been in use as feed additives in agriculture for decades. Driven by the need for new drugs to fight against resistant strains (e.g., vancomycin-resistant entercocci), Rhône-Poulenc Rorer improved the drug-like properties of pristinamycin, culminating in semisynthetic streptogramins—Dalfopristin (type A) and Quinupristin (type B) (Figure 23.7). The two