the treatment several infections. These broad-spectrum synthetic antimetabolites were eventually replaced by natural product antibiotics (e.g., penicillin) with greater potency. Renewed interest stems from their application in combination therapy with trimethoprim (see co-trimoxazole; Table 23.3).

23.6.2 Trimethoprim

Trimethoprim (Figure 23.5) is a pyrimidine derivative whose antibacterial activity was discovered in the early 1960s. In 1968, Bushby and Hitchings showed that trimethoprim is a sulfonamide potentiator. Although it can be used individually, it has up to 100-fold synergistic effect in combination with sulfonamide.

23.7 ANTIBIOTICS AFFECTING PROTEIN BIOSYNTHESIS

Ribosomes (cellular particles, 200–500 Å in diameter) are the protein-synthesizing factories of the cell. Up to 70,000 ribosomes are present in a fast-growing *E. coli* cell in rich growth media, and some of them associate with the plasma membrane on various proteinaceous receptors. All ribosomes comprise a small and a large subunit. In prokaryotes, the assembled ribosome (termed 70S; derived from the sedimentation coefficient) consists of 30 and 50S subunits. The 30S subunit contains a 16S RNA that traps messenger RNAs through their Shine–Dalgarno sequences. The 50S subunit contains a 23S and a 5S RNA molecule and is the site of peptide bond formation catalyzed by the 23S ribozyme. The ribosomes of eukaryotic cells are larger (80S) with 60 and 40S subunits. Several ribosomes can simultaneously translate one mRNA (polyribosome).

Many clinically useful antibiotics bind at or near the peptidyltransferase center (PTC) on the 50S subunit, where the peptide bond formation occurs. On the 30S subunit, the binding sites are clustered along the path of the mRNA and tRNAs (Table 23.2).

Puromycin, an antibiotic isolated from *Streptomyces alboniger* in 1953, although not in clinical use, has been very useful in the study of protein synthesis due to its resemblance to the aminoacyl-adenosine part of aminoacyl-tRNA.

23.7.1 Inhibitors of the 30S Ribosomal Subunit

23.7.1.1 Aminoglycosides

Aminoglycosides are amino sugars connected via glycosidic bonds typically to a 2-deoxystreptamine core. This is the only class of protein synthesis inhibitors that is broadly bactericidal. However, all aminoglycosides present a certain toxicity: vestibular disturbance, with problems of equilibrium, and cochleotoxicity which may result in partial and total loss of hearing. Hence, they are antibiotics of last resort. Many aminoglycosides are natural products, for example, streptomycin, gentamicin, and sisomicin.

Streptomycin (Figure 23.7), the first aminoglycoside discovered (1944; *Streptomyces griseus*), was active mainly against Gram$^-$ bacteria and served as a useful complement to early penicillins. Streptomycin and *p*-aminosalicylic acid were the first drugs used for tuberculosis.

Semisynthetic aminoglycosides were optimized for reduced toxicity (in particular, ototoxicity and nephrotoxicity). An example is amikacin, a semisynthetic derivative of kanamycin clinically introduced in 1976.

After a decline in interest due to toxicity and resistance, there is now a renewed interest in this group due to the need for antibiotics against multidrug and pandrug-resistant Gram$^-$ pathogens. Plazomicin, a synthetic derivative of sisomicin, is broad spectrum and lacks the toxic side effects as observed in clinical trials (phase II, 2012).