Quinolones also target topoisomerase IV, especially in Gram$^+$ bacteria. Dual targeting has the advantage of low mutation frequencies for drug resistance. Their broad spectrum makes them a highly successful class of antibiotics. They are also used to treat intracellular pathogens due to their ability to enter the Gram$^-$ outer membrane via porins. Delafloxacin and finafloxacin are among the quinolones in late clinical trials, e.g., showing increased potency against Gram$^+$ bacteria including MRSA.

23.6 ANTIBIOTICS AFFECTING METABOLIC PATHWAYS

The folate biosynthesis pathway: Folic acid is the precursor for tetrahydrofolate, an important one-carbon unit donor in many biosynthetic pathways, including nucleic acid synthesis. Bacteria build up the folate skeleton de novo, unlike humans who assimilate folate from their diet. Sulfonamides (sulfa drugs) and Trimethoprim target the bacterial folate pathway at different stages (Figure 23.6). The effect of each individual antibiotic is bacteriostatic; the combination is synergistic and bactericidal.

23.6.1 Sulfa Drugs

The sulfa drugs have a common aryl sulfonamide moiety. The first prodrug, prontosil rubrum (1932), is metabolized in the liver to sulfanilamide. Sulfanilamide (1936) (Figure 23.5) proved effective in

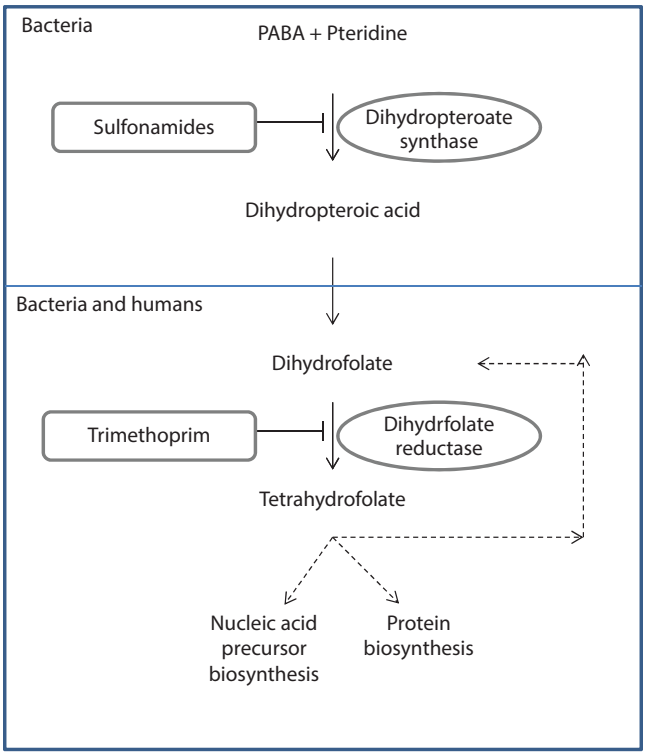

FIGURE 23.6 Sequential inhibition of folate biosynthesis by sulfonamide/trimethoprim. Bacteria build their folate skeleton from the start unlike humans. Sulfonamides competitively inhibit the enzyme dihydropteroate synthase (absent in humans) by mimicking *p*-aminobenzoic acid (PABA), one of the normal constituents of folic acid. Trimethoprim is a highly selective active site inhibitor of the bacterial dihydrofolate reductase enzyme (essential in humans but structurally different enough to allow selective inhibition). The overall effect is depletion of tetrahydrofolate, a carrier for one-carbon units, necessary for many biosynthetic pathways.