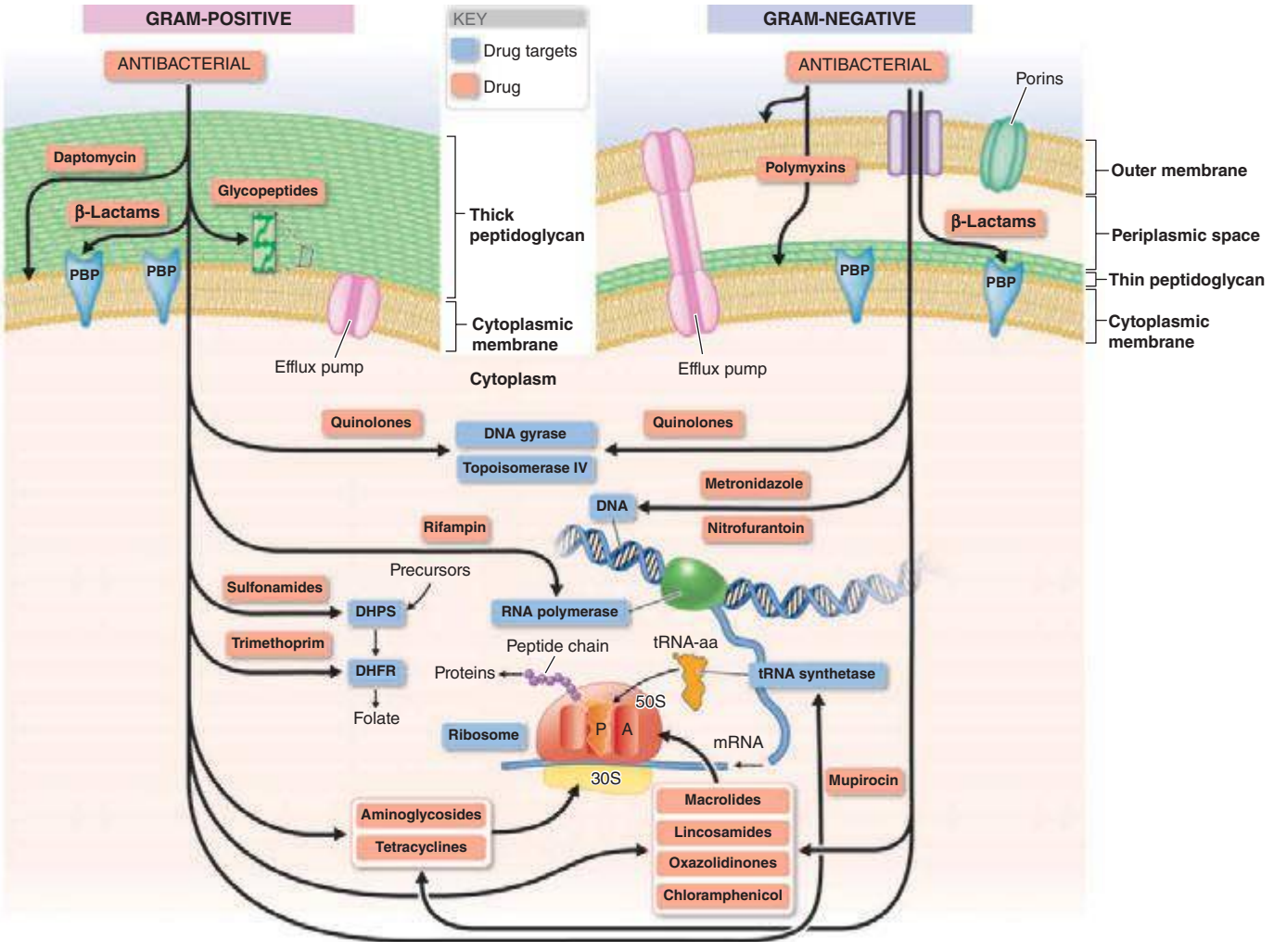

FIGURE 170-1 **Antibacterial targets.** A, aminoacyl site; DHFR, dihydrofolate reductase; DHPS, dihydropteroate synthetase; P, peptidyl site; PBP, penicillin-binding protein; tRNA-aa, aminoacyl tRNA.

from the ribosome. The combination is bactericidal, but macrolide-resistant bacteria exhibit cross-resistance to quinupristin, and the remaining activity of dalfopristin alone is bacteriostatic.

CHLORAMPHENICOL Chloramphenicol binds reversibly to the 23S rRNA of the 50S subunit in a manner that interferes with the proper positioning of the aminoacyl component of tRNA in the A site. This site of binding is near those of the macrolides and lincosamides.

OXAZOLIDINONES Linezolid and tedizolid are the only oxazolidinones in clinical use. They bind directly to the A site in the 23S rRNA of the 50S ribosomal subunit and block binding of aminoacyl tRNA, inhibiting the initiation of protein synthesis.

MUPIROCIN Mupirocin (pseudomonic acid) is used topically. It competes with isoleucine for binding to isoleucyl tRNA synthetase, depleting stores of isoleucyl tRNA and thereby inhibiting protein synthesis.

Inhibition of Bacterial Metabolism Available inhibitors (antimetabolites) target the pathway for synthesis of folate, which is a cofactor in a number of one-carbon transfer reactions involved in the synthesis of some nucleic acids, including pyrimidine, thymidine, and all purines (adenine and guanine), as well as some amino acids (methionine and serine) and acetyl coenzyme A (CoA). Two sequential steps in folate synthesis are targeted. The selective antibacterial effect stems from the inability of mammalian cells to synthesize folate; they depend instead on exogenous sources. Antibacterial activity, however, may be reduced in the presence of high exogenous concentrations of the end products of the folate pathway (e.g., thymidine and purines) that may occur in some infections, resulting from local breakdown of leukocytes and host tissues.

SULFONAMIDES Sulfonamides, including sulfadiazine, sulfisoxazole, and sulfamethoxazole, inhibit dihydropteroate synthetase, which adds *p*-aminobenzoic acid (PABA) to pteridine, producing dihydropteroate. Sulfonamides are structural analogues of PABA and act as competing enzyme substrates.

TRIMETHOPRIM Subsequent steps in folate synthesis are catalyzed by dihydrofolate synthase, which adds glutamate to dihydropteroate, and dihydrofolate reductase, which then generates the final product, tetrahydrofolate. Trimethoprim is a structural analogue of pteridine and inhibits dihydrofolate reductase. Trimethoprim is available alone but is most often used in combination products that also contain sulfamethoxazole and thus block two sequential steps in folate synthesis.

Inhibition of DNA and RNA Synthesis or Activity A variety of antibacterial agents act on these processes.

QUINOLONES The quinolones include nalidixic acid, the first agent in the class, and newer, more widely used fluorinated derivatives (fluoroquinolones), including norfloxacin, ciprofloxacin, levofloxacin, moxifloxacin, and gemifloxacin. The quinolones are synthetic compounds that inhibit bacterial DNA synthesis by interacting with the DNA complexes of two essential enzymes, DNA gyrase and DNA topoisomerase IV, which alter DNA topology. Quinolones trap enzyme–DNA complexes in such a way that they block movement of the DNA replication apparatus and can generate lethal double-strand breaks