Table 17.1 Examples of Enzyme Inhibitors Used in the Treatment of Bacterial, Fungal, Viral, and Parasitic Diseases

Clinical Use	Enzyme Inhibited	Inhibitor
Antibacterial	Dihydropteroate synthetase	Sulphonamides
Antibacterial	Dihydrofolate reductase	Trimethoprim, methotrexate
Antibacterial	Alanine racemase	D-Cycloserine
Antibacterial	Transpeptidase	Penicillins, cephalosporins
Antifungal	Fungal sterol 14α-demethylase	Clotrimazole, ketoconazole
Antifungal	Fungal squalene epoxidase	Terbinafine, naftifine
Antiviral	Thymidine kinase and thymidylate kinase	Idoxuridine
Antiviral	DNA, RNA polymerases	Cytosine arabinoside (Ara-C)
Antiviral	Viral DNA polymerase	Acyclovir, vidarabine
Antiviral	HIV reverse transcriptase	Dideoxyinosine, zidovudine
Antiviral	HIV protease	Saquinavir
Antiviral	Influenza virus neuraminidase	Zanamavir, oseltamivir
Antiprotozoal	Pyruvate dehydrogenase	Organoarsenical agents
Antiprotozoal	Ornithine decarboxylase	a-Difluoromethylornithine

velopment of the sulfa drugs (sulfonamides), enzyme inhibitors have played a vital role in controlling these infectious agents. Table 17.1 provides a list of enzyme inhibitors that have been used in the treatment of the various diseases caused by these agents. All these compounds needed to satisfy the usual requirements for specificity and low toxicity.

This can be achieved in a variety of ways. For instance, it is possible to inhibit an essential pathway in the pathogen that does not exist in the host. D-Cycloserine **(1)** (Fig. 17.1), for example, inhibits alanine racemase, an enzyme involved in bacterial cell wall biosynthesis and not found in humans (8, 9). D-Cycloserine is active against a broad spectrum of both gram-positive and gram-negative bacteria (10), but plays its major role in the treatment of tuberculosis (11). Conversely, even if both host and pathogen contain the same enzymes, it may be possible to exploit subtle structural differences between the isozymes to obtain a highly specific inhibitor that preferentially binds to the invader's version. Trimethoprim (2) shows this selective toxicity. An inhibitor of dihydrofolate reductase, trimethoprim is a potent antibacterial agent because the bacterial enzyme is inhibited at a concentration several thousand times lower than that required for inhibition of the mammalian isozyme (12). Acyclovir (**3a**), an antiviral drug used for the treatment of herpes infections **(13,** 14), also fits into this category. It binds very tightly to the ***Herpes simplex*** DNA polymerase with an estimated half-life of about 40 days. Acyclovir is a prodrug because it requires transformation by a viral thymine kinase and cellular phosphotransferases to the corresponding triphosphate (**3b**) to serve ***in vivo*** as an inhibitor of the viral DNA polymerase **(15).**

Table 17.2 Examples of Enzyme Inhibitors Used in the Treatment of Cancer

Type of Cancer	Enzyme Inhibited	Inhibitor
Benign prostatic hyperplasia	Steroid 5α-reductase	Finasteride
Estrogen-mediated breast cancer	Aromatase	Arninoglutethimide, fadrozole
Leukemia, osteosarcoma, head, neck, and breast cancer	Dihydrofolate reductase	Methotrexate
Colorectal cancer	Thymidylate synthase	5-Fluorouracil
Leukemia	Glutamine-PRPP amidotransferase	6-Mercaptopurine, azathioprine
Small-cell lung cancer, non-Hodgkin's lymphoma	Topoisomerase II	Etoposide
Hairy-cell leukemia	Adenosine deaminase	Pentostatin