Table 17.3 Examples of Enzyme Inhibitors Used in Various Human Disease States

Clinical Use	Enzyme Inhibited	Inhibitor
Epilepsy	GABA transaminase	γ-Vinyl GABA
Epilepsy	Carbonic anhydrase	Sulthiame
Epilepsy	Succinic semialdehyde dehydrogenase	Sodium valproate
Antidepressant	Monoamine oxidase (MAO)	Tranylcypromine, phenelzine
Antihypertensive	Angiotensin converting enzyme	Captopril, enalaprilat
Cardiac disorders	Na^+,K^+-ATPase	Cardiac glycosides
Gout	Xanthine oxidase	Allopurinol
Ulcer	H^+,K^+-ATPase	Omeprazole
Hyperlipidemia	HMG-CoA reductase	Atorvastatin, simvastatin
Anti-inflammatory	Prostaglandin synthase, Cyclooxygenase (COX) I and II	Aspirin, naproxen, ibuprofen
Arthritis	Cyclooxygenase (COX) II	Celecoxib
Glaucoma	Acetylcholinesterase	Neostigmine
Glaucoma	Carbonic anhydrase II	Acetazolamide, dichlorphenamide

Although their inhibitors are not specifically therapeutic agents in themselves, the p-lactamases are another important target for drug design. These are bacterial enzymes and, as with the alanine racemases, are not found in humans. Inhibitors of β-lactamases include clavulanic acid (4) (16–20) and sulbactam (penicillanic acid sulfone) (5) (18, 21–24). These two compounds act to prevent the bacterial degradation of penicillins and cephalosporins by p-lactamases, thereby extending their lifetime and effectiveness. Accordingly, both clavulanic acid (4) and sulbactam (5) have reached the market as drugs that act synergistically with these commonly prescribed antibacterial agents.

Even though it has proved possible to selectively inhibit the enzymes of a number of pathogens, the enzymes of cancer cells have proved to be a far more elusive target. Indeed, the majority of the currently employed antitumor agents can be described as antiproliferative agents. These take advantage of the fact that many, but not all, tumor cells grow and divide more rapidly than normal cells. Lymphomas, for example, proliferate more rapidly than solid tumors, whereas, conversely, acute leukemia cells divide more slowly than the surrounding bone marrow cells. Most of the enzyme inhibitors used as these antiproliferative agents (Table 17.2) can also be described as antimetabolites (i.e., they inhibit a metabolic pathway), often those involved in DNA biosynthesis, which are important for cell survival or replication. 5-Fluorouracil (6), the prodrug form of an inactivator of thymidylate synthase (25), and methotrexate (7), an inhibitor of dihydrofolate reductase (26, 27), both fit into this category. Unfortunately, rapidly dividing normal cells, such as hair follicles, the cells lining the gastrointestinal tract, and the bone marrow cells involved in the immune system are also significantly affected. The resultant hair loss, nausea, and susceptibility to infection means that this type of chemotherapy is seldom employed as a first-line defense against cancer.

The inhibition of enzymes involved in metabolic pathways is not restricted to anticancer agents. A variety of diseases have been correlated with either the dysfunction of an enzyme or an imbalance of metabolites. A cross section of the disease states treated with enzyme inhibitors is shown in Table 17.3. Practically, these may be treated by the inhibition of an individual enzyme or by using enzyme inhibitors to regulate the metabolite concentration in the body. For example, an imbalance of the two neurotransmitters, glutamate and γ-aminobutyric acid, is responsible for the convulsions observed in epileptic seizure. The latter is metabolized by y-aminobutyric acid aminotransferase (GABA-T) and, consequently, inhibitors of this enzyme offered themselves as potential antiepileptic candidates. This led to the development of the GABA-T inhibitor, vigabatrin (8)(28), which clinically results in an increase of the brain concentration of γ-aminobutyric acid and cessation of epileptic convulsions. As with the anticancer agents, block-