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THE POTENTIAL USE OF MECHANISM-BASED ENZYME INACTIVATORS IN MEDICINE

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Mechanism-based enzyme inactivators are unreactive compounds that bear a structural similarity to a substrate or product of a specific enzyme. Once at the active site, the target enzyme converts, generally via its normal catalytic mechanism, into a product that usually forms a covalent bond to the enzyme. If this class of enzyme inactivators is compared with another class of potent enzyme inactivators, the affinity labeling agents, then the advantages of mechanism-based enzyme inactivators as potential drugs become apparent. Affinity labeling agents are reactive compounds that often bear a structural similarity to a substrate for an enzyme and typically undergo alkylation and acylation reactions with active-site nucleophiles in target enzymes. Because of their reactivity, they can react not only with the target enzyme but also with other enzymes and biomolecules, leading to toxicity (many cancer chemotherapeutic drugs, for example, are affinity labeling agents). A mechanism-based enzyme inactivator, on the other hand, is an unreactive compound, so non-specific alkylations should not occur. Ideally, only the target enzyme will be capable of catalyzing the appropriate conversion of the inactivator to the activated species, and inactivation will result with every turnover. This latter situation can be quite important for potential drug use. If the activated species in released from the active site, it may react with another biomolecule, since, following activation, it would be an affinity labeling agent. Alternatively, the released product itself may be toxic or may be metabolized to a toxic species. Consequently, the ideal partition ratio, i.e., the ratio of the number of inactivator molecules converted to a product and released per inactivation event, is zero. Under these ideal conditions, the inactivator would be a strong drug candidate, because it should be highly specific and low in toxicity. In fact α-difluoromethylornithine, a specific mechanism-based inactivator of ornithine decarboxylase used in the treatment of protozoal infections, has been administered in amounts of 30 g per day for several weeks with only minor side effects.[1]

Despite the great potential of mechanism-based enzyme inactivators as drugs, there are no drugs on the American drug market today that were rationally designed as mechanism-based inactivators of specific enzymes. That is not to say that no drugs are

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mechanism-based enzyme inactivators; only that the ones that are in current medical use were determined *ex post facto* to be mechanism-based inactivators. The list of current drugs that are mechanism-based enzyme inactivators includes the antidepressant agents, tranylcypromine and phenelzine, the antihypertensive agents, hydralazine and pargyline, and the antiparkinsonian drug, deprenyl (all of which inactivate monoamine oxidase); clavulanic acid, a compound used to protect penicillins and cephalosporins against bacterial degradation (inactivates β-lactamases); the antitumor drug, 5-fluoro-2′-deoxyuridylate and the antiviral agent, 5-trifluoromethyl-2′-deoxyuridylate (both of which inactivate thymidylate synthetase); the uricosuric agent, allopurinol (inactivates xanthine oxidase); the antithyroid drugs, methimazole, methylthiouracil, and propylthiouracil (thyroid peroxidase); and the antibiotic, chloramphenicol, the antifertility drug, norethindrone, the anaesthetics, halothane and fluoroxene, the sedative, ethclorvynol, the diuretic and antihypertensive agent, spironolactone, the pituitary suppressant, danazol, and the hypnotic, novonal (all of which inactivate cytochrome P-450). These drugs that inactivate cytochrome P-450, however, do not derive their medicinal effect as a result of that inactivation. The first two rationally-designed mechanism-based enzyme inactivator drugs to be given U.S. drug approval may be 4-amino-5-hexenoic acid (γ-vinyl GABA; vigabatrin; inactivates γ-aminobutyric acid aminotransferase) and α-difluoromethylornithine (eflornithine; inactivates ornithine decarboxylase), which are in latter stages of clinical trials for the treatment of seizures and protozoal infections, respectively.

The selection of appropriate target enzymes for mechanism-based enzyme inactivator design depends upon the same criteria as those for any type of enzyme

TABLE I
Enzymes with potential use in medicine already targeted for mechanism-based inactivation

Enzyme	Therapeutic Goal
S-adenosylhomocysteine hydrolase	antiviral agent
alanine racemase	antibacterial agent
D-amino acid aminotransferase	antibacterial agent
γ-aminobutyric acid aminotransferase	anticonvulsant agent
arginine decarboxylase	antibacterial agent
aromatase	anticancer agent
L-aromatic amino acid decarboxylase	synergistic with antiparkinson drug
dihydrofolate reductase	anticancer agent; antibacterial agent; antiprotozoal agent
dihydroorotate dehydrogenase	antiparasitic agent; anticancer agent
DNA polymerase I	antiviral agent
dopamine β-hydroxylase	antihypertensive agent; pheochromocytoma agent
histidine decarboxylase	antihistamine; anti-ulcer agent
β-lactamase	synergistic with antibiotics
monoamine oxidase	antidepressant agent; antihypertensive agent; antiparkinsonian agent
ornithine decarboxylase	anticancer agent; antiprotozoal agent
serine proteases	treatment of emphysema, inflammation, arthritis, adult respiratory distress syndrome, anticoagulant agent, pancreatitis, certain degenerative skin disorders, antiviral agent, and digestive disorders.
testosterone 5α-reductase	anticancer agent
thymidylate synthetase	anticancer agent
xanthine oxidase	uricosuric agent

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inhibitor; that is, to diminish the concentration of a particular enzyme product (e.g., uric acid from xanthine) or to increase the concentration of an enzyme substrate (e.g., block the catabolism of γ-aminobutyric acid). In the case of a bacterial or tumor enzyme, inactivation may prevent important metabolic processes from taking place and this can result in growth inhibition. Examples of enzymes with potential use in medicine that already have been targeted for mechanism-based enzyme inactivation and the therapeutic goals of inactivation are listed in Table I. Mechanism-based enzyme inactivators that have been designed for these enzymes are tabulated in this review and representative literature citations are noted. Associated with each table is a brief description of why inactivation of that particular enzyme leads to the desired therapeutic effect. A more comprehensive in-depth review and discussion of mechansim-based enzyme inactivation in general, its chemistry and enzymology, is forthcoming.[2]

S-Adenosyl-L-homocysteine Hydrolase Inactivation

It has been found that adenosylhomocysteine (AdoHcy) competitively inhibits most of the methyltransferases that utilize *S*-adenosylmethionine as the methyl donating agent. This inhibition, apparently, is a mechanism for regulation of these enzymes. Inhibition of *S*-adenosyl-L-homocysteine hydrolase, the enzyme that degrades adenosylhomocysteine,* results in an accumulation of AdoHcy which inhibits growth and replication of various viruses, particularly those requiring a methylated 5′-cap structure on their mRNA's. In Table II are summarized various mechanism-based inactivators of AdoHcy hydrolase. The enzyme sources used for the inactivation studies include human splenic lymphoblasts, calf liver, beef liver, rat liver, mouse liver, hamster liver, and mouse L1210 cells.

TABLE II
Mechanism-based inactivators of *S*-adenosyl-L-homocysteine hydrolase

Compound	Reference
2′-deoxyadenosine	3–5
adenine arabinoside	3
5′-deoxyadenosine	3
5′-deoxy-5′thiomethyladenosine	3
3′-deoxyadenosine	3
carbocyclic adenosine	6
other nucleoside analogues	7
adenosine	8, 9
erythro-9-(2-hydroxynon-3-yl)adenosine	9
ara-A	10
9-β-D-arabinofuranosyladenine 5′-monophosphate	10
9-β-D-arabinofuranosyladenine 5′-triphosphate	10
9-β-D-arabinofuranosyl-2-fluoroadenine	11
5′- and 2-substituted adenosines	12
neplanocin A	13, 14

*Actually, the equilibrium of this reaction lies in favor of the synthesis of adenosylhomocysteine, but *in vivo*, the adenosine and L-homocysteine are rapidly transformed, thus driving the reaction in the opposite direction.

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TABLE III
Mechanism-based inactivators of alanine racemase

Compound	Reference
β-fluoroalanine	15–19
O-carbamoyl-D-serine	17, 20
O-acetyl-D-serine	17, 18, 20
β-chloroalanine	17, 18, 20
β,β-dichloroalanine	19
β,β-difluoroalanine	21
β,β,β-trifluoroalanine	21
D- and L-β-fluoroalanine	20
β-chloro-D- and -L-alanine	22

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Alanine Racemase Inactivation

Some of the alanine residues that comprise bacterial cell walls have the D-configuration. Since the natural amino acids in proteins have the L-configuration, bacteria need to biosynthesize the required D-alanine. Alanine racemase is an important enzyme for the production of D-alanine; consequently, inactivation of this enzyme, an enzyme not found in mammalian sources, is an ideal target for design of an antibacterial agent. A summary of mechanism-based inactivators of alanine racemase is shown in Table III. The inactivation studies were carried out using enzyme from *E. coli* B, *S. typhimurinum* (*alr* gene), *S. typhimurium* (*dad* B gene), *P. putida*, and various other bacteria.

D-Amino Acid Aminotransferase Inactivation

Certain D-amino acids, particularly D-glutamic acid, that are essential for the formation of the peptidoglycan layer of the bacterial cell wall, are biosynthesized by transamination of the corresponding α-keto acids rather than by racemization of the L-amino acid. Inactivation of D-amino acid aminotransferase blocks the formation of these essential cell wall constituents. Mechanism-based inactivators of D-amino acid aminotransferase are summarized in Table IV. Inactivation studies were performed on enzyme from *B. sphaericus*.

γ-Aminobutyric Acid Aminotransferase Inactivation

Convulsions can arise from an imbalance in two neurotransmitters in the brain, glutamate, an excitatory neurotransmitter, and γ-aminobutyric acid (GABA), an

TABLE IV
Mechanism-based inactivators of D-amino acid aminotransferase

Compound	Reference
β-fluoroalanine	23
β-chloro-D-alanine	24
β-bromo-D-alanine	25
β-cyano-D-alanine	26

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inhibitory neurotransmitter. If a convulsion is induced in an animal and GABA is injected into the brain, the convulsions cease. However, GABA is ineffective when administered peripherally, because it does not cross the blood-brain barrier, a membrane that protects the brain from xenobiotics and other undesirable substances. An approach to the design of anticonvulsant agents has been to prepare compounds capable of crossing the blood-brain barrier and that inactivate γ-aminobutyric acid aminotransferase (GABA-T), the enzyme that degrades GABA. Provided that the compound does not also inactivate glutamate decarboxylase, another pyridoxal phosphate (PLP)-dependent enzyme that catalyzes the conversion of glutamate to GABA, it should be an effective method of raising the *in vivo* GABA levels in the brain. In Table V are summarized mechanism-based inactivators of GABA aminotransferase. Enzyme sources for inactivation studies include *P. fluorescens, E. coli,* and brains from pig, rat, rabbit, mouse, cat, and monkey.

Arginine Decarboxylase Inactivation

The polyamines, spermidine and spermine, and their precursor, putrescine, are important regulators of cell division, growth, and differentiation. The principal biosynthetic pathway is initated by the conversion of ornithine to putrescine, but an alternative

TABLE V
Mechanism-based inactivators of γ-aminobutyric acid aminotransferase

Compound	Reference
(*S*)-4-amino-5-halopentanoic acids	27, 28
3-amino-4-fluorobutanoic acid	29, 30
4-amino-5-fluoropentanoic acid	29
5-amino-6-fluorohexanoic acid	29
(*S*, *E*)-4-amino-5-fluoropent-2-enoic acid	31
(E)-4-amino-5-fluoropent-2-enoic acid	32
5-fluoro-4-oxopentanoic acid	33
3-amino-4,4-difluorobutanoic acid	29, 34
4-amino-5,5-difluoropentanoic acid	29
5-amino-6,6-difluorohexanoic acid	29
3-amino-2,4-difluorobutanoic acid	29, 34
3-amino-4-chloro-4-fluorobutanoic acid	34
(*Z*)- and (E)-4-amino-3-halobut-2-enoic acids (except the (*Z*)-3-chloro analogue)	35
ethanolamine *O*-sulfate	36
4-aminohex-5-ynoic acid	37–39
3-amino-4-pentynoic acid	29
4-amino-5-hexynoic acid	29
5-amino-6-heptynoic acid	29
(*S*)-4-amino-5, 6-heptadienoic acid	40
(*S*)-4-amino-5-hexenoic acid	41
(*E*)-4-amino-2, 5-hexadienoic acid	32
4-amino-5-fluoro-5-hexenoic acid	42
(*Z*)-4-amino-6-fluoro-5-hexenoic acid	42
4-amino-6, 6-difluoro-5-hexenoic acid	42
4-amino-5, 6, 6-trifluoro-5-hexenoic acid	42
5-amino-1, 3-cyclohexadienyl-1-carboxylic acid (gabaculine)	43
3-amino-1, 5-cyclohexadienyl-1-carboxylic acid (isogabaculine)	44
(*R*, *S*)-4-amino-4, 5-dihydrofuran-2-carboxylic acid	45
(*R*, *S*)-4-amino-4, 5-dihydrothiophene-2-carboxylic acid	46
4-amino-3-isoxazolidinone (cycloserine)	47

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TABLE VI
Mechanism-based inactivators of arginine decarboxylase

Compound	Reference
α-(difluoromethyl)arginine	48, 49
α-(monofluoromethyl)arginine	49
(*E*)-α-(monofluoromethyl)dehydroarginine	49
α-(monofluoromethyl)agmatine	49
α-ethynylagmatine	49
α-allenylagmatine	49

pathway, which is important in many microorganisms and plants, is the conversion of arginine to agmatine (catalyzed by arginine decarboxylase) and agmatine to putrecine (agmatine amidinohydrolase or agmatine iminohydrolase). Therefore, if arginine decarboxylase is blocked, polyamine synthesis should be inhibited. However, arginine decarboxylase inhibition generally results in increased ornithine decarboxylase activity in order to compensate for diminished putrescine biosynthesis. It appears necessary, then, to inhibit both decarboxylases to achieve decreased polyamine biosynthesis and affect cell growth. Mechanism-based inactivators of arginine decarboxylase are summarized in Table VI. The sources of the enzyme for inactivation work are oats, barley, *E. coli* and other bacteria.

Aromatase Inactivation

Aromatase is the enzyme that catalyzes the conversion of androgens to estrogens, which are essential hormones for reproduction and development, but also promote the growth of various breast cancers. Inhibition of this enzyme is an effective approach to cancer chemotherapy. Table VII summarizes mechanism-based inactivators of aromatase. Inactivation studies have been carried out with enzyme from human placenta, human trophoblast choriocarcinoma, and rat ovary.

TABLE VII
Mechanism-based inactivators of aromatase

Compound	Reference
norethisterone	50
norethisterone acetate	51
19-ethynyl-substituted androst-4-ene-3,17-diones	52–55
10β-allenyl-substituted androst-4-ene--3,17-diones	52–54
17β-hydroxy-10-methylthioestra-1,4-dien-3-one	56
19,19-difluoroandrost-4-ene-3,17-dione	57
17β-hydroxy-10β-mercaptoestr-4-en-3-one	58
19-mercaptoandrost-4-ene-3,17-dione	58
4-androstene-3,6,17-trione	59, 60
1,4,6-androstatriene-3,17-dione	59, 60
4-androstene-19-ol-3,6,17-trione	60
3,6,17-trioxoandrost-4-en-19-al	60
4-hydroxy- and 4-acetoxy-4-androstene-3,17-dione	60, 61
1,4-androstadiene-3,17-dione	62
testolactone	62
7α-(4′-amino)phenylthio-1,4-androstadiene-3,17-dione	63

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L-Aromatic Amino Acid Decarboxylase Inactivation

Parkinson's disease is a degenerative neurological disorder characterized by chronic, progressive motor dysfunction resulting in tremors, rigidity, and akinesia. The symptoms arise from a degeneration of dopamine receptors and a markedly reduced concentration of L-aromatic amino acid decarboxylase. Both of these problems result in low brain levels of the inhibitory neurotransmitter dopamine, resulting in the observed symptoms. Since dopamine does not cross the blood-brain barrier, its peripheral administration is not effective for increasing brain dopamine levels. However, L-dopa is actively transported into the brain where it is converted to dopamine by L-aromatic amino acid decarboxylase. One major complication with L-dopa therapy arises from the fact that L-aromatic amino acid decarboxylase also exists in the periphery, and more than 95% of the L-dopa administered is decarboxylated in its first pass through the liver and kidneys. Combination therapy with an inactivator of peripheral L-aromatic amino acid decarboxylase by a compound that cannot cross the blood-brain barrier would be synergistic with L-dopa and potentiate the effectiveness of this antiparkinsonian drug.

Also, several types of cancers contain endocrine cells that are rich in dopa decarboxylase. It is not clear what the function of this is, but inactivation of the enzyme may be a useful approach to cancer chemotherapy. Mechanism-based inactivators of L-aromatic amino acid decarboxylase are summarized in Table VIII. Enzyme sources for inactivation studies include pig kidney, human pheochromocytoma, and various bacteria. A recent review[64] of inhibitors of this enzyme summarizes much of the mechanistic work on this enzyme.

Dihydrofolate Reductase Inactivation

Tetrahydrofolate, a cofactor involved in the transfer of one-carbon units to a wide

TABLE VIII
Mechanism-based inactivators of L-aromatic amino acid decarboxylase

Compound	Reference
(*R*)-α-(monofluoromethyl)dopamine	16
α-(difluoromethyl)dopamine	16, 65
α-(trifluoromethyl)dopamine	16
α-(monofluoromethyldopa	16, 66–69
(*S*)-α-(monofluoromethyl)tyrosine	16, 67
α-(difluoromethyl)dopa	16, 70
α-(monochloromethyl)dopa	64
α-(monofluoromethyl)-2,3-dihydroxyphenylalanine	64
α-(difluoromethyl)-2,3-dihydroxyphenylalanine	64
α-(monofluoromethyl)-2,5-dihydroxyphenylalanine	64
α-(difluoromethyl)-2,5-dihydroxyphenylalanine	64
α-(monofluoromethyl)-2-hydroxyphenylalanine	64
α-(monofluoromethyl)-3-hydroxyphenylalanine	64
α-(monofluoromethyl)-4-hydroxyphenylalanine	64
α-(monofluoromethyl)-5-hydroxytryptophan	64
α-(difluoromethyl)-5-hydroxytryptophan	64
α-(ethynyl)dopa	71
α-(allenyl)dopa	72
α-(vinyl)dopa	71
α-(allenyl)phenylalanine	73

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TABLE IX
Mechanism-based inactivators of dopamine β-hydroxylase

Compound	Reference
2-X-3-(*p*-hydroxyphenyl)-1-propenes (X = H, Br, Cl)	77
3-arylpropenes	78
3-(*p*-substituted phenyl)propynes	79
1-(*p*-substituted benzyl)cyclopropanes	79
phenylhydrazine	80
1-phenyl-1-propyne	81
1-amino-2-aryl-2-propenes	82–84
3-phenylpropargylamine	83, 84
α-methylstyrene	83
α-(cyanomethyl)styrene	83
3-hydroxy-α-methylstyrene	83
N-phenylethylenediamine	83, 85
N-methyl-*N*-phenylethylenediamine	83, 85
aniline and substituted anilines	85
β-chlorophenethylamine	86
p-hydroxybenzyl cyanide	87, 88
m- and *p*-substituted benzyl cyanides	88
phenylacetaldehyde	89
p-hydroxyphenylacetamide	89
phenylacetamide	89
β-hydroxyphenylacetaldehyde	89
p-cresol	90
m-cresol	90
4-methylcatechol	90
4-ethylphenol	90
3-hydroxybenzyl alcohol	90

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variety of substrates, is generated by dihydrofolate reductase-catalyzed reduction of dihydrofolate. Various enzymes involved in the *de novo* biosynthesis of purine nucleotides and deoxythymidylate, precursors to DNA, require tetrahydrofolate-derived cofactors. Thymidylate synthetase (*vide infra*), which catalyzes the last step in the *de novo* biosynthesis of deoxythymidylate, an essential nucleotide for DNA biosynthesis, utilizes 5,10-methylenetetrahydrofolate, which is converted to dihydrofolate during the enzyme-catalyzed reaction. Therefore, if dihydrofolate reductase is inactivated, it blocks deoxythymidylate and, therefore, DNA biosynthesis. The rationalization for inactivator selectivity of tumor cell enzymes in favor of normal cell enzymes is discussed in the thymidylate synthetase section. There are innumerable reversible inhibitors and affinity labeling inactivators of dihydrofolate reductase, but recently the first mechansim-based inactivator, 2-amino-7,8-dihydro-6-hydroxymethyl-7-spirocyclopropylpteridin-4(3*H*)-one, was reported.[74]

Dihydroorotate Dehydrogenase Inactivation

Dihydroorotate dehydrogenase is one of the enzymes in the biosynthetic pathway to pyrimidines. Inactivation of this enzyme blocks the biosynthesis of orotic acid, a precursor of deoxythymidylate which, as discussed in the section on thymidylate synthetase inactivation, is required for DNA biosynthesis. (*S*,*S*)- and (*R*,*R*)-3-(1-Carboxy-2-phenylethyl)-5-benzylhydantoins are time-dependent inactivators of this enzyme.[74a]

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DNA Polymerase I Inactivation

Inactivation of DNA polymerase I, the enzyme that catalyzes the biosynthesis of DNA, blocks this essential process for growth and replication. Since this enzyme also is important to man, it is essential that selectivity for DNA polymerase I of the foreign organism is achieved. Two compounds have been targeted for the enzyme from herpes simplex virus, *E. coli*, and human sources. They are 9-[(2-hydroxyethoxy)methyl]-guanine (acyclovir) triphosphate[75] and adenosine 2′,3′-riboepoxide 5′-triphosphate.[76]

Dopamine β-Hydroxylase Inactivation

Dopamine β-hydroxylase catalyzes the conversion of dopamine to norepinephrine, a neurotransmitter that constitutes 10–20% of the catecholamine content of human adrenal medulla and as much as 97% in some pheochromocytomas. Norepinephrine acts as a vasoconstrictor and, therefore, raises the blood pressure. Inactivation of dopamine β--hydroxylase blocks the biosynthesis of norepinephrine, and, thereby, attenuates the cardiovascular effects of this catecholamine. The release of norepinephrine, resulting in vasoconstriction, during removal of phenochromocytomas, also could be prevented by administration of a dopamine β-hydroxylase inactivator. Mechanism-based inactivators of dopamine β-hydroxylase are summarized in Table IX. The enzyme used in these studies comes from bovine adrenal medulla.

Histidine Decarboxylase Inactivation

Histamine is known to interact with two receptors, known as the H_1- and H_2 receptors. Interaction of histamine with the H_1 receptor elicits contraction of various smooth muscles, e.g., of the bronchi and gut, and can stimulate various sensory nerve endings. These effects can produce allergic or hypersensitivity reactions. Interaction of histamine with the H_2 receptor stimulates gastric acid secretion, leading to ulceration. Most histamine in mammalian tissues arises from decarboxylation of histidine. Therefore, inactivation of histidine decarboxylation appears to be a viable approach to decrease the concentration of histamine. A summary of mechanism-based inactivators of histidine decarboxylase is given in Table X. The enzymes from hamster placenta, human peripheral blood leukocytes, *Morganella morganii* AM-15, and rat liver, hypothalamus, gastric mucosa, brain, and stomach have been used in the inactivation studies.

β-Lactamase Inactivation

The penicillins are potent antibiotics that have proven to be wonder drugs for the treatment of a wide variety of bacterial infections. They act as affinity labeling agents for transpeptidase, the bacterial enzyme that catalyzes the cross linking of the cell wall peptidoglycan. However, various penicillin-resistant strains of bacteria are now prevalent. The resistance to these β-lactam-containing drugs can result from the production of an enzyme, called β-lactamase, that catalyzes the hydrolysis of the β-lactam ring of penicillins, thereby deactivating them. Compounds that inactivate β-lactamases, then, would destroy the natural defenses of the penicillin-resistant bacteria, and make them susceptible to the action of penicillin. β-Lactamase inactivators, then, are not antibiotics in their own right, but are synergistic with penicillins

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TABLE X
Mechanism-based inactivators of histidine decarboxylase

Compound	Reference
(*R*)- and (*S*)-α-(monofluoromethyl)histamine	16
α-(trifluoromethyl)histamine	91
α-ethynylhistamine	92
(*S*)-α-(monofluoromethyl)histidine	93–100
α-(monochloromethyl)histidine	101

and render the penicillins effective against these strains of bacteria. Mechanism-based inactivators of various bacterial β-lactamases are summarized in Table XI. Other recent reviews of β-lactamase inhibitors have been published.[102,103]

Monoamine Oxidase Inactivators

Monoamine oxidase (MAO) is one of the enzymes responsible for the catabolism of biogenic amines. It has been found in chronically depressed individuals that the brain concentrations of various biogenic amines are depleted. Consequently, compounds that inhibit MAO increase the biogenic amine pool and exhibit an antidepressant effect. MAO inhibitors have been used in the treatment of depression for about 25 years; however, there is a potent toxic effect associated with their use that resulted in the death of a few of the early patients taking these drugs. The toxicity is a cardiovascular effect which was shown to result from the consumption of certain foods with a high tyramine content while taking these drugs. Tyramine triggers the release of norepinephrine which is a vasoconstrictor, and this raises the blood pressure. If a drug is being taken that blocks the degradation of norepinephrine, the blood pressure can continue to rise until, eventually, a hypertensive crisis can result. Once this was determined, the MAO inhibitor drugs were put back on the market, but only with strict dietary regulations. Because of this toxic effect, little advancement in the development of MAO inhibitors occurred until recently. MAO is known to exist in

TABLE XI
Mechanism-based inactivators of β-lactamase

Compound	Reference
6-acetylmethylenepenicillanic acid	104
(Z)-6-(methoxymethylene)penicillanic acid	105
penam sulfones	106
6β-(trifluoromethanesulfonyl)amidopenicillanic acid sulfone	107
6β-(trifluoromethanesulfonyl)-*N*-methyl)amidopenicillanic acid sulfone	108
6β-(substituted sulfonyl)amidopenicillanic acid sulfones	109
6-(2-pyridyl)methylenepenicillanic acid sulfone	110
penicillanic acid sulfone	107, 111–114
(α-hydroxybenzyl)penicillanic acid sulfones	115, 116
6β-bromopencillanic acid	117–119
6β-iodopenicillanic acid	119, 120
clavulanic acid	113, 121–124
clavulanic acid analogues	123, 125, 126
olivanic acids	127–130
asparenomycins	131
PS-5	132

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TABLE XII
Mechanism-based inactivators of monoamine oxidase

Compound	Reference
propynylamine	133
N-benzyl-*N*-methyl-2-propynylamine (pargyline)	134–136
pargyline analogues	137–144
clorgyline	145
deprenyl	145
N, *N*-dimethylpropynylamine	146
N-2, 3-butadienyl-*N*-benzyl-*N*-methylamine	147, 148
α-allenic amines	147, 149
allylamine	150, 151
2-amino-3-butene	150, 152
1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)	153, 154
1-methyl-4-phenyl-2, 3-dihydropyridinium ($MPDP^+$)	153
(*E*)-2-(3, 4-dimethoxyphenyl)-3-fluoroallylamine	155
(*E*)- and (*Z*)-2-aryl-3-fluoro- and -2-aryl-3, 3-difluoroallylamines	156
other fluoroallylamines	157–159
cis-3-chloroallylamine	150
(*E*)-2-phenyl-3-haloallylamine	156
3-bromoallylamine	160
3-{4-[(3-chlorophenyl)methoxy]phenyl}-5-[(methylamino)methyl] 2-oxazolidinone	161
trans-2-phenylcyclopropylamine (tranylcypronine)	162, 163
trans-2-phenylcyclopropylamine analogues	134, 163, 164
N-(phenoxyethyl)cyclopropylamines	165–167
5-phenyl-3-(*N*-cyclopropyl)ethylamine-1, 2, 4-oxadiazole and analogues	168, 169
N-cyclopropylbenzylamine	170
N-cyclopropyl-α-methylbenzylamine	171
N-(1-methylcyclopropyl)benzylamine	152
1-phenylcyclopropylamine	172, 173
1-benzylcyclopropylamine	174
1-phenylcyclobutylamine	175
phenylhydrazine	176, 177
benzylhydrazine	178
2-phenylethylhydrazine(phenelzine)	176, 179
1-methyl-2-phenylethylhydrazine	176
(2-chloro)phenylethylamine	180

two isozymic forms called MAO A and MAO B. The differences in the two forms is their effectiveness in degrading the various biogenic amines. If only one of these isozymes is inhibited, then the increase in biogenic amines could occur leading to the antidepressant effect, but the other form would be available to degrade excessive tyramine or norepinephrine, thereby preventing the toxic cardiovascular effect. This approach is now possible, and highly selective inhibitors have been shown to be effective drugs without a cardiovascular effect. There is much promise for these second generation MAO inhibitors in the safe treatment of depression.

As described under L-aromatic amino acid decarboxylase inactivation, increasing the brain concentration of dopamine is a goal for antiparkinsonism. MAO inhibitors are effective agents to increase the concentration of various biogenic amines and also are being used in combination with L-dopa therapy. Various mechanism-based inactivators of MAO are summarized in Table XII. Inactivation experiments were

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TABLE XIII
Mechanism-based inactivators of ornithine decarboxylase

Compound	Reference
α-(monofluoromethyl)putresine	181, 182
(*E*)-2,5-diamino-1-fluoropent-3-ene	181, 183
α-(difluoromethyl)putrescine	181, 182
(*E*)-2,5-diamino-1,1-difluoropent-3-ene	183
5-hexyne-1,4-diamine	184
2-methyl-6-heptyne-2,5-diamine	185
6-heptyne-2,5-diamine	185
(2*R*,5*R*)-6-heptyne-2,5-diamine	181, 185
(*E*)-2-hexen-5-yne-1,4-diamine	186
(*R*)- and (*S*)-α-allenylputrescine	187
α-(monofluoromethyl)ornithine	181, 188
(*E*)-2,5-diamino-2-fluoromethylpent-3-enoic acid	181, 183
α-(difluoromethyl)ornithine	189
(*E*)-2,5-diamino-2-difluoromethylpent-3-enoic acid	183
α-(monochloromethyl)ornithine	190
α-(cyanomethyl)ornithine	190
α-ethynylornithine	191
α-vinylornithine	191

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carried out with enzymes from livers of pig, beef, human, and rat, from brains of pig, human, and rat, from beef kidney, from rat, hepatoma, and from human placenta.

Ornithine Decarboxylase Inactivators

As indicated in the arginine decarboxylase section, the polyamines, spermidine and spermine, and their precursor, putrescine, are important regulators of cell division, growth, and differentation. Ornithine decarboxylase, the enzyme that catalyzes the conversion of ornithine to putrescine, is the rate-limiting step in polyamine biosynthesis. Consequently, inactivation of that enzyme shuts down much of the production of the polyamines. Although the initial goal was to use this approach for cancer chemotherapy, it has now been found to be more effective in the treatment of parasitic infestations. Table XIII lists various mechanism-based inactivators of ornithine decarboxylase. Sources of the enzyme used in activation work include rat liver, kidney, and prostate, mouse kidney, *E. coli*, *P. aeruginosa*, *Trypanosoma brucei brucei*, *Physarum* A, B, and *C. thermohydrosulfuricum*.

Serine Protease Inactivation

It has been hypothesized that a cause for pulmonary emphysema is an imbalance in certain proteases and protease inhibitors in the lungs. Human leukocyte elastase and cathepsin G are believed to be released by neutrophils in the lungs to digest dead lung tissue and destroy foreign bacteria. Inhibitors of these enzymes also are released to prevent these enzymes from destroying elastin and lung connective tissue. When, for various reasons, the protease inhibitors are deficient, uncontrolled proteolysis of lung connective tissue can occur, resulting in emphysema. Inactivators of elastase and cathepsin G, therefore, would substitute for the natural inhibitors. Another target protease is thrombin, the enzyme that catalyzes the conversion of fibrinogen into

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TABLE XIV
Mechanism-based inactivators of serine proteases

Compound	Reference
(*E*)-ynenol lactones	193
3-chloroisocoumarin	194, 195
3,3-dichlorophthalide	194, 195
3,4-dichloroisocoumarin	195
3-acetoxyisocoumarin	195
3-benzyl- and 3-methyl-6-chloro-2-pyrones	196
7-amino-4-chloro-3-(m)ethoxyisocoumarin	197, 198
7-amino-4-chloro-3-(2-phenylethoxy)isocoumarin	199
isatoic anhydride and substituted 3*H*-1,3-oxazine,-2,6-diones	200, 201
imidazole *N*-carboxamides	202
N-(1*H*-imidazol-1-ylcarbonyl)amino acid methyl ester derivatives	203
aryl azolide analogues	204
carbonyl sulfonate salts of amino acid esters	205
3-benzyl-*N*-(methanesulfonyloxy)succinimide	206
N-(methoxysuccinyl)-Ala-Ala-Pro-ValCH_2Cl	207

fibrin which aggregates into blood clots. Inactivation of this enzyme would lead to an anticoagulant effect. A review of inhibitors of elastase and cathepsin G has recently appeared.[192] Mechanism-based inactivators of these enzymes are listed in Table XIV. The two sources of this enzyme used are human leukocytes and porcine pancreas.

Testosterone 5α-Reductase Inactivation

Testosterone is reduced by testosterone 5α-reductase to the more active androgen, 5α-dihydrotestosterone, which mediates androgenic activity in various organs and glands. Compounds that inactivate this enzyme may be useful for averting excessive effects of androgenic action in disease such as acne, hirsutism, male pattern baldness, prostate hypertrophy, and prostate cancer. Reversible inhibitors have not been effective in maintaining sufficient inhibition of the enzyme to observe the effects. Because of the instability of this enzyme, few approaches to its inactivation have been made. (5α, 20*R*)-4-Diazo-21-hydroxy-20-methylpregnan-3-one is a time-dependent inactivator of rat prostate testosterone 5α-reductase.[208]

Thymidylate Synthetase Inactivation

Thymidylate synthetase catalyzes the conversion of deoxyuridylate to deoxythymidylate, an important precursor to DNA. Because thymidylate synthetase is the last enzyme in the *de novo* pathway for deoxythymidylate production, inactivation of this enzyme in tumor cells blocks the prodcution of deoxythymidylate and, therefore, DNA biosynthesis. However, normal cells also require thymidylate synthetase for *de novo* synthesis of deoxythymidylate. In rapidly proliferating cells, such as tumor cells, the requirement for DNA precursors is greatly elevated; therefore, there is increased activity of thymidylate synthetase. Since tumor cells take up DNA precursors and produce others more rapidly than do normal cells, selective toxicity of the tumor enzyme is possible. The design of selective inactivators of thymidylate synthetase, then, constitutes an important approach to cancer chemotherapy. Mechanism-based inactivators of thymidylate synthetase are listed in Table XV. Inactivation experi-

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TABLE XV
Mechanism-based inactivators of thymidylate synthetase

Compound	Reference
5-fluoro-2′-deoxyuridine monophosphate	209–214
1-(5-phosphono-β-D-arabinofuranosyl)-5-fluorouracil	215
2′, 5-difluoro-1-arabinosyluridylate	216
N^4-hydroxy-2′-deoxycytidylic acid	217
5-trifluoromethyl-2′-deoxyuridylate	218
trans-5-(3, 3, 3-trifluoro-1-propenyl)-2′-deoxyuridylate	219
5-ethynyl-2′-deoxyuridylate	220

ments have been carried out on enzyme from *L. casei*, *E. coli*, *S. faecalis*, Ehrlich ascites carcinoma, human lymphoblastic leukemia, and chick embryo.

Xanthine Oxidase Inactivation

Xanthine oxidase catalyses the oxidation of xanthine to uric acid, which is excreted through the kidneys. At physiological pH, uric acid is fairly insoluble, and tends to form supersaturated solutions. When this point is exceeded, uric acid crystallizes in the joints and connective tissues, a condition known as gout. One solution to this problem is to inactivate xanthine oxidase to halt the production of uric acid. This would allow the crystallized uric acid to have an opportunity to be redissolved. Allopurinol is a noncovalent mechanism-based inactivator of bovine milk xanthine oxidase.[221]

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