The Organic Chemistry of Drug Design and Drug Action

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To Mom and the memory of Dad,
for their warmth, their humor, their ethics, their inspiration,
but mostly for their genes.

CHAPTER 3

Receptors

I. Introduction

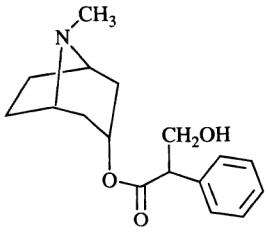
Up to this point in our discussion it appears that a drug is taken, and by some kind of magic it travels through the body and elicits a pharmaceutical effect. *Pharmacokinetics* (absorption, distribution, metabolism, and excretion) was mentioned in Chapter 2, but no discussion was presented regarding what produces the pharmaceutical effect. The site of drug action, which is ultimately responsible for the pharmaceutical effect, is called a *receptor*. The interaction of the drug with the receptor constitutes *pharmacodynamics*. In this chapter the emphasis is placed on pharmacodynamics of general noncatalytic receptors, in Chapter 4 a special class of receptors that have catalytic

properties, called enzymes, will be discussed, and in Chapter 6 another receptor, DNA, will be the topic of discussion. The drug–receptor properties described in this chapter also apply to drug–enzyme and drug–DNA complexes.

II. Receptor Structure

A. Historical

In 1878 John N. Langley,[1] a physiology student at Cambridge University, while studying the mutually antagonistic action of the alkaloids atropine (**3.1**; now used as an antisecretory agent) and pilocarpine (**3.2**; used in the treatment of glaucoma, but causes sweating and salivation) on cat salivary flow, suggested that both of these chemicals interacted with some substance in the nerve endings of the gland cells. Langley, however, did not follow up this notion for over 25 years.



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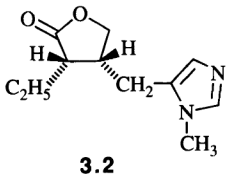


3.2

Paul Ehrlich[2] suggested his *side chain theory* in 1897. According to this hypothesis, cells have side chains attached to them that contain specific groups capable of combining with a particular group of a toxin. Ehrlich termed these side chains receptors. Another facet of this hypothesis was that when toxins combined with the side chains, excess side chains were produced and released into the bloodstream. In today's biochemical vernacular these excess side chains would be called *antibodies*, and they combine with toxins stoichiometrically.

In 1905 and 1906 Langley[3] studied the antagonistic effects of curare (a generic term for a variety of South American quaternary alkaloid poisons that cause muscular paralysis) on nicotine stimulation of skeletal muscle. He concluded that there was a receptive substance that received the stimulus and, by transmitting it, caused muscle contraction. This was really the first time that attention was drawn to the two fundamental characteristics of a receptor, namely, a *recognition capacity* for specific ligands and an *amplification component*, the ability of the ligand–receptor complex to initiate a biological response.

B. What Is a Receptor?

In general, receptors are integral proteins (i.e., polypeptide macromolecules) that are embedded in the phospholipid bilayer of cell membranes (see Fig. 2.3). They, typically, function in the membrane environment; consequently, their properties and mechanisms of action depend on the phospholipid milieu. Vigorous treatment of cells with detergents is required to dissociate these proteins from the membrane. Once they become dissociated, however, they can lose their integrity. Since they generally exist in minute quantities and can be unstable, few receptors have been purified, and little structural information is known about them. Advances in molecular biology more recently have permitted the isolation, cloning, and sequencing of receptors,[4] and this is leading to further approaches to molecular characterization of these proteins. However, these receptors, unlike many enzymes, are still typically characterized in terms of their function rather than by their structural properties. The two functional components of receptors, the recognition component and the amplification component, may represent the same or different sites on the same protein. Various hypotheses regarding the mechanism by which drugs may initiate a biological response are discussed in Section III,E.

III. Drug–Receptor Interactions

A. General Considerations

In order to appreciate mechanisms of drug action it is important to understand the forces of interaction that bind drugs to their receptors. Because of the low concentration of drugs and receptors in the bloodstream and other biological fluids, the law of mass action alone cannot account for the ability of small doses of structurally specific drugs to elicit a total response by combination with all, or practically all, of the appropriate receptors. One of my all-time favorite calculations, shown below, supports the notion that something more than mass action is required to get the desired drug–receptor interaction.[5] One mole of a drug contains 6.02×10^{23} molecules (Avogadro's number). If the molecular weight of an average drug is 200 g/mol, then 1 mg (often an effective dose) will contain $6.02 \times 10^{23}(10^{-3})/200 = 3 \times 10^{18}$ molecules of drug. The human organism is composed of about 3×10^{13} cells. Therefore, each cell will be acted upon by $3 \times 10^{18}/3 \times 10^{13} = 10^5$ drug molecules. One erythrocyte cell contains about 10^{10} molecules. On the assumption that the same number of molecules is found in all cells, then for each drug molecule, there are $10^{10}/10^5 = 10^5$ molecules of the human body! With this ratio of human molecules to drug molecules, Le Chatelier would have a difficult time explaining how the drug could interact and form a stable complex with the desired receptor.

The driving force for the drug–receptor interaction can be considered as a low-energy state of the drug–receptor complex [Eq. (3.1)], where k_{on} is the rate constant for formation of the drug–receptor complex, which depends on the concentrations of the drug and the receptor, and k_{off} is the rate constant for breakdown of the complex, which depends on the concentration of the drug–receptor complex as well as other forces. The biological activity of a drug is related to its affinity for the receptor, which is measured by its K_D, the dissociation constant at equilibrium [Eq. (3.2)]. Note that K_D is a *dissociation* constant, so that the smaller the K_D, the larger the concentration of the drug–receptor complex, and the greater is the affinity of the drug for the receptor.

$$\text{Drug} + \text{receptor} \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} \text{drug–receptor complex} \tag{3.1}$$

$$K_D = \frac{[\text{drug}][\text{receptor}]}{[\text{drug–receptor complex}]} \tag{3.2}$$

B. Forces Involved in the Drug–Receptor Complex

The forces involved in the drug–receptor complex are the same forces experienced by all interacting organic molecules and include covalent bonding, ionic (electrostatic) interactions, ion–dipole and dipole–dipole interactions, hydrogen bonding, charge-transfer interactions, hydrophobic interactions, and van der Waals interactions. Weak interactions usually are possible only when molecular surfaces are close and complementary, that is, bond strength is distance dependent. The spontaneous formation of a bond between atoms occurs with a decrease in free energy, that is, ΔG is negative. The change in free energy is related to the binding equilibrium constant (K_{eq}) by Eq. (3.3). Therefore, at physiological temperature (37°C) changes in free energy of -2 to -3 kcal/mol can have a major effect on the establishment of good secondary interactions. In fact, a decrease in $\Delta G°$ of -2.7 kcal/mol changes the binding equilibrium constant from 1 to 100. If the K_{eq} were only 0.01 (i.e., 1% of the equilibrium mixture in the form of the drug–receptor complex), then a $\Delta G°$ of interaction of -5.45 kcal/mol would shift the binding equilibrium constant to 100 (i.e., 99% in the form of the drug–receptor complex).

$$\Delta G° = -RT \ln K_{eq} \tag{3.3}$$

In general, the bonds formed between a drug and a receptor are weak noncovalent interactions; consequently, the effects produced are reversible. Because of this, a drug becomes inactive as soon as its concentration in the extracellular fluids decreases. Often it is desirable for the drug effect to last only a limited time so that the pharmacological action can be terminated. In the case of CNS stimulants and depressants, for example, a prolonged action

could be harmful. Sometimes, however, the effect produced by a drug should persist, and even be irreversible. For example, it is most desirable for a *chemotherapeutic agent*, a drug that acts selectively on a foreign organism or tumor cell, to form an irreversible complex with its receptor so that the drug can exert its toxic action for a prolonged period.[6] In this case, a covalent bond would be desirable.

In the following subsections the various types of possible drug–receptor interactions are discussed briefly. These interactions are applicable to all types of receptors, including enzymes and DNA, that are described in this book.

1. Covalent Bonds

The *covalent bond* is the strongest bond, generally worth anywhere from −40 to −110 kcal/mol in stability. It is seldom formed by a drug–receptor interaction, except with enzymes and DNA. These bonds will be discussed further in Chapters 5 and 6.

2. Ionic (or Electrostatic) Interactions

For protein receptors at *physiological pH* (generally taken to mean pH 7.4), basic groups such as the amino side chains of arginine, lysine, and, to a much lesser extent, histidine are protonated and, therefore, provide a cationic environment. Acidic groups, such as the carboxylic acid side chains of aspartic acid and glutamic acid, are deprotonated to give anionic groups.

Drug and receptor groups will be mutually attracted provided they have opposite charges. This *ionic interaction* can be effective at distances farther than those required for other types of interactions, and they can persist longer. A simple ionic interaction can provide a $\Delta G^\circ = -5$ kcal/mol which declines by the square of the distance between the charges. If this interaction is reinforced by other simultaneous interactions, the ionic interaction becomes stronger ($\Delta G^\circ = -10$ kcal/mol) and persists longer. Acetylcholine is used as an example of a molecule that can undergo an ionic interaction (Fig. 3.1).

3. Ion–Dipole and Dipole–Dipole Interactions

As a result of the greater electronegativity of atoms such as oxygen, nitrogen, sulfur, and halogens relative to that of carbon, C—X bonds in drugs and receptors, where X is an electronegative atom, will have an asymmetric distribution of electrons; this produces electronic dipoles. The dipoles in a drug molecule can be attracted by ions (*ion–dipole interaction*) or by other dipoles (*dipole–dipole interaction*) in the receptor, provided charges of opposite sign are properly aligned. Since the charge of a dipole is less than that of an ion, a

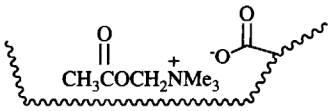


Figure 3.1. Example of a simple ionic interaction. The wavy line represents the receptor surface.

dipole–dipole interaction is weaker than an ion–dipole interaction. In Fig. 3.2 acetylcholine is used to demonstrate these interactions, which can provide a $\Delta G°$ of -1 to -7 kcal/mol.

4. Hydrogen Bonds

Hydrogen bonds are a type of dipole–dipole interaction formed between the proton of a group X—H, where X is an electronegative atom, and other electronegative atoms (Y) containing a pair of nonbonded electrons. The only significant hydrogen bonds occur in molecules where X and Y are N, O, or F. X removes electron density from the hydrogen so it has a partial positive charge, which is strongly attracted to nonbonded electrons of Y. The interaction is denoted as a dotted line, —X—H····Y—, to indicate that a covalent bond between X and H still exists, but that an interaction between H and Y also occurs. When X and Y are equivalent in electronegativity and degree of ionization, the proton can be shared equally between the two groups, that is, —X····H····Y—.

The hydrogen bond is unique to hydrogen because it is the only atom that can carry a positive charge at physiological pH while remaining covalently bonded in a molecule, and hydrogen also is small enough to allow close approach of a second electronegative atom. The strength of the hydrogen bond is related to the Hammett σ constants.[7]

There are *intramolecular* and *intermolecular* hydrogen bonds; the former are stronger (see Fig. 3.3). Hydrogen bonding can be quite important for biological activity. For example, methyl salicylate (**3.3**), an active ingredient

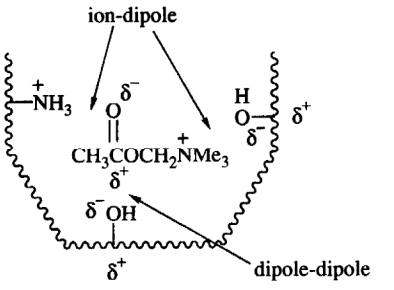


Figure 3.2. Examples of ion–dipole and dipole–dipole interactions. The wavy line represents the receptor surface.

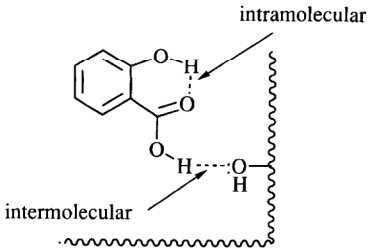
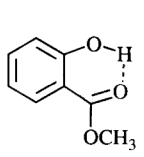


Figure 3.3. Examples of hydrogen bonds. The wavy lines represents the receptor surface.

in many muscle pain remedies and at least one antiseptic, is a weak antibacterial agent. The corresponding para isomer, methyl *p*-hydroxybenzoate (**3.4**), however, is considerably more active as an antibacterial agent and is used as a food preservative. It is believed that the antibacterial activity of **3.4** is derived from the phenolic hydroxyl group. In **3.3** this group is masked by intramolecular hydrogen bonding.[8]



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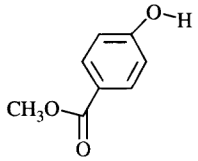


3.4

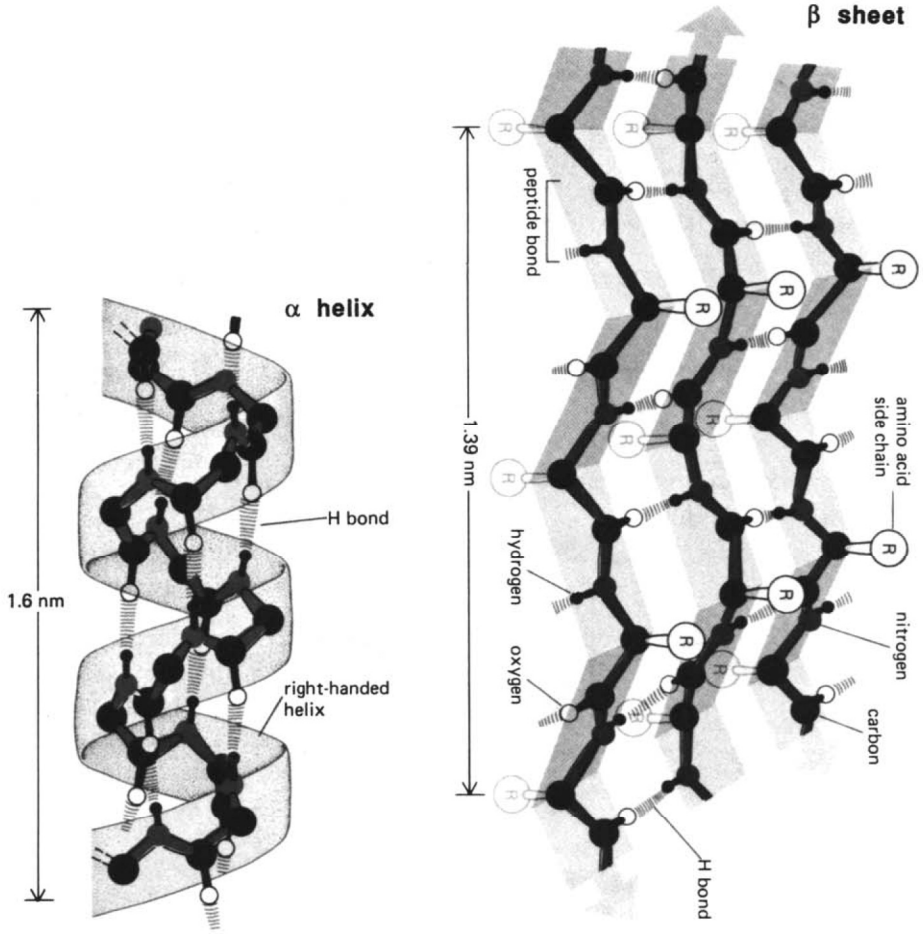
Hydrogen bonds are essential in maintaining the structural integrity of α-helix and β-sheet conformations of peptides and proteins (**3.5**)[1] and the double helix of DNA (**3.6**).[2] As discussed in Chapter 6, many antitumor agents act by intercalation into the DNA base pairs or by alkylation of the DNA bases, thereby preventing hydrogen bonding. This disrupts the double helix and destroys the DNA.

Another instance where hydrogen bonding is suggested to be important arises when the potency of various oxygen-containing drugs becomes reduced by substitution of a sulfur atom for the oxygen atom in the drug. Sulfur, which is very poor at hydrogen bonding relative to oxygen, presumably cannot interact with the receptor group that hydrogen bonds to the oxygen, and drug–receptor complex stability becomes diminished.

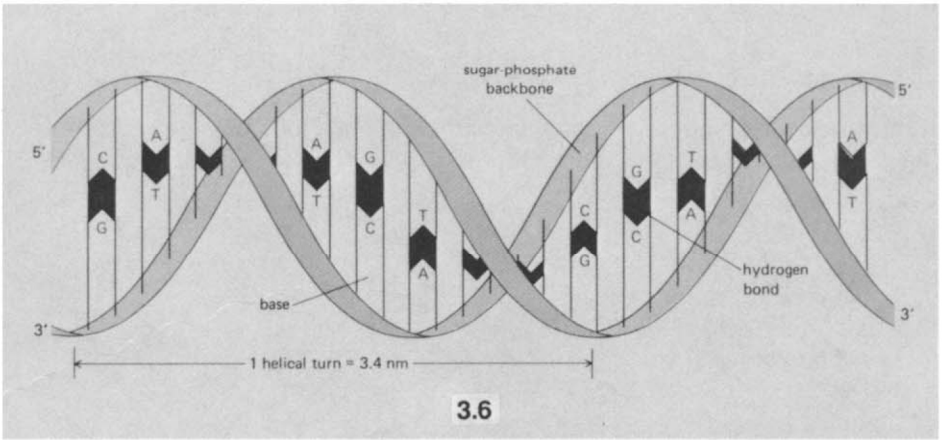
The $\Delta G°$ for hydrogen bonding can be between -1 and -7 kcal/mol but usually is in the range of -3 to -5 kcal/mol.

[1] From B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts, and J. D. Watson, "Molecular Biology of the Cell," 2nd Ed., pp. 110 and 109, respectively, Garland Publishing, New York, 1989, with permission. Copyright © 1989 Garland Publishing.

[2] From B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts, and J. D. Watson, "Molecular Biology of the Cell," 2nd Ed., p. 99. Garland Publishing, New York, 1989, with permission. Copyright © 1989 Garland Publishing.


β sheet
α helix
1.6 nm
H bond
right-handed helix
1.39 nm
peptide bond
amino acid side chain
hydrogen
oxygen
nitrogen
carbon
H bond
R

3.5


sugar-phosphate backbone
5'
3'
base
hydrogen bond
1 helical turn = 3.4 nm

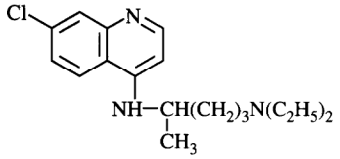
3.6

5. Charge-Transfer Complexes

When a molecule (or group) that is a good electron donor comes into contact with a molecule (or group) that is a good electron acceptor, the donor may transfer some of its charge to the acceptor. This forms a *charge-transfer complex*, which, in effect, is a molecular dipole–dipole interaction. The potential energy of this interaction is proportional to the difference between the ionization potential of the donor and the electron affinity of the acceptor.

Electron donors contain π-electrons, for example, alkenes, alkynes, and aromatic moieties with electron-donating substituents, or groups that have a pair of nonbonded electrons, such as oxygen, nitrogen, and sulfur moieties. Acceptor groups contain electron-deficient π orbitals, for example, alkenes, alkynes, and aromatic moieties having electron-withdrawing substituents, or weakly acidic protons. There are groups on receptors that can act as electron donors, such as the aromatic ring of tyrosine or the carboxylate group of aspartate, as electron acceptors, such as cysteine, and electron donors and acceptors, such as histidine, tryptophan, and asparagine.

Charge-transfer interactions are believed to provide the energy for intercalation of certain planar aromatic antimalarial drugs, such as chloroquine (**3.7**), into parasitic DNA (see Chapter 6). The fungicide, chlorothalonil, is shown in Fig. 3.4 as a hypothetical example for a charge-transfer interaction with a tyrosine.



3.7

The $\Delta G°$ for charge-transfer interactions also can range from -1 to -7 kcal/mol.

6. Hydrophobic Interactions

In the presence of a nonpolar molecule or region of a molecule, the surrounding water molecules orient themselves and, therefore, are in a higher energy

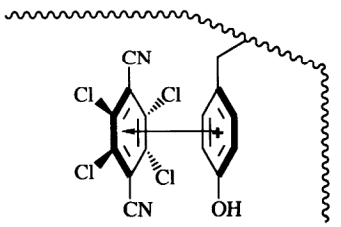


Figure 3.4. Example of a charge-transfer interaction. The wavy line is the receptor surface.

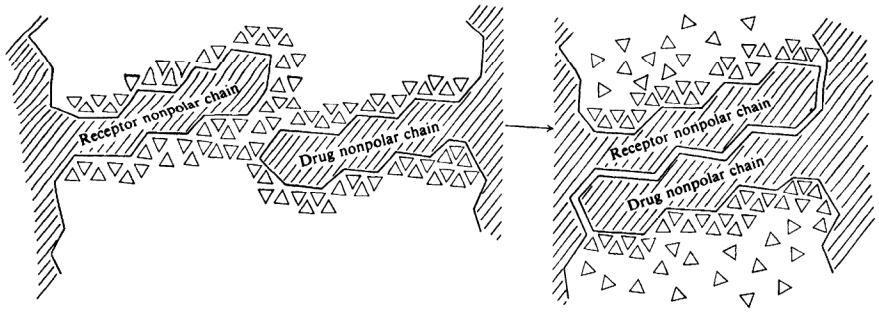


Figure 3.5. Formation of hydrophobic interactions. (Reprinted with permission of John Wiley & Sons, Inc. from Korolkovas, A. 1970. "Essentials of Molecular Pharmacology," p. 172. Wiley, New York. Copyright © 1970. John Wiley & Sons, Inc. and by permission of Kopple, K. D. 1966. "Peptides and Amino Acids." Addison-Wesley, Reading, Massachusetts.)

state than when only other water molecules are around. When two nonpolar groups, such as a lipophilic group on a drug and a nonpolar receptor group, each surrounded by ordered water molecules, approach each other, these water molecules become disordered in an attempt to associate with each other. This increase in entropy, therefore, results in a decrease in the free energy that stabilizes the drug–receptor complex. This stabilization is known as a *hydrophobic interaction* (see Fig. 3.5). Consequently, this is not an attractive force of two nonpolar groups "dissolving" in one another but, rather, is the decreased free energy of the nonpolar group because of the increased entropy of the surrounding water molecules. Jencks[9] has suggested that hydrophobic forces may be the most important single factor responsible for noncovalent intermolecular interactions in aqueous solution. Hildebrand,[10] on the other hand, is convinced that hydrophobic effects do not exist. Every methylene-methylene interaction (which actually may be a van der Waals interaction; see Section III,B,7) liberates 0.7 kcal/mol of free energy. In Fig. 3.6 the topical anesthetic butamben is depicted in a hypothetical hydrophobic interaction with an isoleucine group.

7. Van der Waals or London Dispersion Forces

Atoms in nonpolar molecules may have a temporary nonsymmetrical distribution of electron density which results in the generation of a temporary dipole.

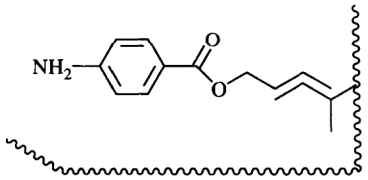


Figure 3.6. Example of hydrophobic interactions. The wavy line represents the receptor surface.

As atoms from different molecules (such as a drug and a receptor) approach each other, the temporary dipoles of one molecule induce opposite dipoles in the approaching molecule. Consequently, an intermolecular attraction, known as *van der Waals forces*, results. These weak universal forces only become significant when there is a close surface contact of the atoms; however, when there is molecular complementarity, numerous atomic interactions (each contributing about −0.5 kcal/mol to the ΔG°) result, which can add up to a significant overall drug–receptor binding component.

8. Conclusion

Since noncovalent interactions are generally weak, cooperativity by several types of interactions is critical. To a first approximation, enthalpy terms will be additive. Once the first interaction has taken place, translational entropy is lost. This results in a much lower entropy loss in the formation of the second interaction. The effect of this cooperativity is that several rather weak interactions may combine to produce a strong interaction. Since several different types of interactions are involved, selectivity in drug–receptor interactions can result. In Fig. 3.7 the local anesthetic dibucaine is used as an example to show the variety of interactions that are possible.

C. Ionization

At physiological pH (pH 7.4), even mildly acidic groups, such as carboxylic acid groups, will be essentially completely in the carboxylate anionic form; phenolic hydroxyl groups may be partially ionized. Likewise, basic groups, such as amines, will be partially or completely protonated to give the cationic form. The ionization state of a drug will have a profound effect not only on its drug–receptor interaction, but also on its partition coefficient (log P; see Section II,E,2,b of Chapter 2).

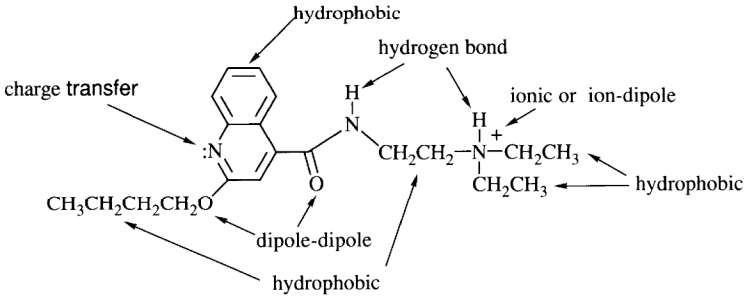
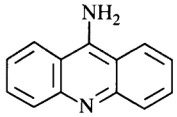


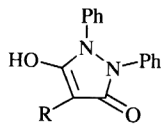
Figure 3.7. Examples of potential multiple drug–receptor interactions. The van der Waals interactions are excluded.

The importance of ionization was recognized in 1924 when Stearn and Stearn[11] suggested that the antibacterial activity of stabilized triphenylmethane cationic dyes was related to an interaction of the cation with some anionic group in the bacterium. Increasing the pH of the medium also increased the antibacterial effect, presumably by increasing the ionization of the receptors in the bacterium. Albert and co-workers[12] made the first rigorous proof that a correlation between ionization and biological activity existed. A series of 101 aminoacridines, including the antibacterial drug, 9-aminoacridine or aminacrine (**3.8**), all having a variety of pK_a values, was tested against 22 species of bacteria. A direct correlation was observed between ionization (formation of the cation) of the aminoacridines and antibacterial activity. However, at lower pH values, protons can compete with these cations for the receptor, and antibacterial activity is diminished. When this was realized, Albert[13] notes, the Australian Army during World War II was advised to pretreat wounds with sodium bicarbonate to neutralize any acidity prior to treatment with aminacrine. This, apparently, was quite effective in increasing the potency of the drug. The mechanism of action of aminoacridines is discussed in Chapter 6.



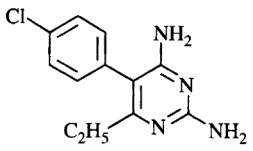
3.8

The great majority of alkaloids which act as neuroleptics, local anesthetics, and barbiturates have pK_a values between 6 and 8; consequently both neutral and cationic forms are present at physiological pH.[13] This may allow them to penetrate membranes in the neutral form and exert their biological action in the ionic form. Antihistamines and antidepressants tend to have pK_a values of about 9. The uricosuric (increases urinary excretion of uric acid) drug phenylbutazone [**3.9**, R = $(CH_2)_3CH_3$] has a pK_a of 4.5 and is active as the anion (the OH proton is acidic). However, since the pH of urine is 4.8 or higher, suboptimal concentrations of the anion were found in the urinary system. Sulfinpyrazone (**3.9**, R = CH_2CH_2SOPh) has a lower pK_a of 2.8 and is about 20 times more potent than phenylbutazone; the anionic form blocks reabsorption of uric acid by renal tubule cells.[14]



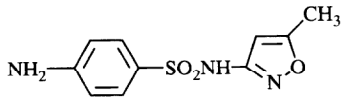
3.9

The antimalarial drug pyrimethamine (**3.10**) has a pK_a of 7.2 and is best absorbed from solutions of sufficient alkalinity that it has a high proportion of molecules in the neutral form (to cross membranes). Its mode of action, the inhibition of the parasitic enzyme dihydrofolate reductase, however, requires that it be in the protonated cationic form.



3.10

Similarly, there are drugs such as the anti-inflammatory agent indomethacin (**2.18**) and the antibacterial agent sulfamethoxazole (**3.11**) whose pharmacokinetics (migration to site of action) depend on their nonionized form, but whose pharmacodynamics (interaction with the receptor) depend on the anionic form (carboxylate and sulfonamido ions, respectively). In a cell-free system the antibacterial activity of **3.11** and other sulfonamides was directly proportional to the degree of ionization, but in intact cells, where the drug must cross a membrane to get to the site of action, the antibacterial activity also was dependent on lipophilicity (the neutral form).[15]



3.11

Up to this point only the ionization of the drug has been considered. As indicated in Section III,B,2, there are a variety of acidic and basic groups on receptors. Anionic groups in DNA include phosphoric acid groups (pK_a 1.5 or 6.5) and purines and pyrimidines (pK_a ~9); anionic groups in proteins are carboxylic acids (aspartic and glutamic acids; pK_a 3.5–5), phenols (tyrosine; pK_a 9.5–11), sulfhydryls (cysteine; pK_a 8.5), and hydroxyls (serine and threonine; pK_a ~13.5). Cationic groups in DNA include amines (adenine and cytidine; pK_a 3.5–4) and in proteins include imidazole (histidine, pK_a 6.5–7), amino (lysine, pK_a ~10), and guanidino (arginine, pK_a ~13) groups. Therefore, the structure and function of a receptor can be strongly dependent on the pH of the medium, especially if an *in vitro* assay is being used. The pK_a values of various groups embedded in a receptor, however, can be quite variable, and will depend on the microenvironment. If a carboxyl group is in a nonpolar region, its pK_a will be raised because the anionic form is destabilized. Glutamate-35 in lysozyme and the lysozyme–glycolchitin complex has a pK_a of 6.5 and 8.2, respectively.[16] If the carboxylate forms a salt bridge, it will be stabi-

lized and its pK_a will be lower. Likewise, an amino group buried in a nonpolar microenvironment will have a lower pK_a because protonation will be disfavored; the ε-amino group of the active site lysine residue in acetoacetate decarboxylase has a pK_a of 5.9.[17] If the ammonium group forms a salt bridge, it will be stabilized, deprotonation will be inhibited, and the pK_a will be raised.

Now that the importance of drug–receptor interactions has been emphasized, we turn our attention to the principal method for the determination of these interactions.

D. Determination of Drug–Receptor Interactions

Hormones and neurotransmitters are important natural compounds that are responsible for the regulation of a myriad of physiological functions. These molecules interact with a specific receptor in a tissue and elicit a specific characteristic response. For example, the activation of a muscle by the central nervous system is mediated by release of the neurotransmitter acetylcholine (ACh; the molecule in Figs. 3.1 and 3.2). If a plot is made of the logarithm of the concentration of the acetylcholine added to a muscle tissue preparation versus the percentage of total muscle contraction, the graph shown in Fig. 3.8 may result. This is known as a *dose–response* or *concentration–response curve*. The low concentration part of the curve results from too few neurotransmitter molecules available for collision with the receptor. As the concentration increases, it reaches a point where a linear relationship is observed between the logarithm of the neurotransmitter concentration and the biological response. As most of the receptors become occupied, the probability of a drug and receptor molecule interacting diminishes, and the curve deviates

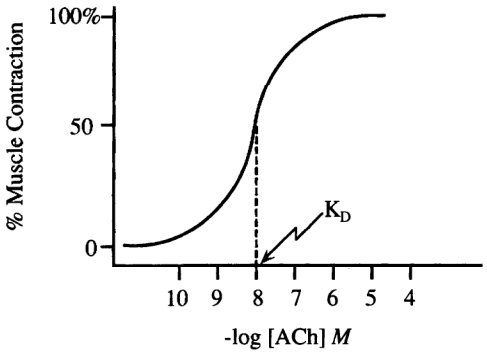


Figure 3.8. Effect of increasing the concentration of a neurotransmitter on muscle contraction.

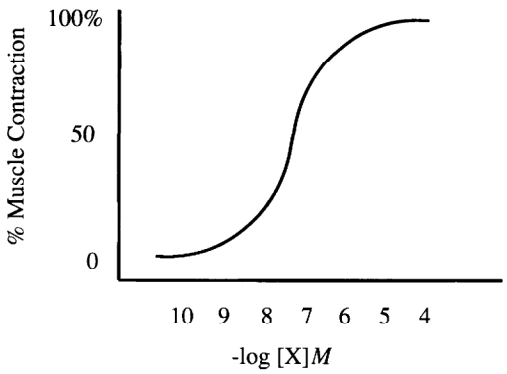


Figure 3.9. Dose–response curve for an agonist.

from linearity (the high concentration end). Dose–response curves are a means of measuring drug–receptor interactions and are the standard method for comparing the potencies of various compounds that interact with a particular receptor. Any measure of a response can be plotted on the ordinate, such as LD_{50}, ED_{50}, or percentage of a physiological effect.

If another compound (X) is added in increasing amounts to the same tissue preparation and the curve shown in Fig. 3.9 results, the compound, which produces the same maximal response as the neurotransmitter, is called an *agonist*. A second compound (Y) added to the tissue preparation shows no response at all (Fig. 3.10A); however, if it is added to the neurotransmitter, the effect of the neurotransmitter is blocked until a higher concentration of the neurotransmitter is added (Fig. 3.10B). Compound Y is called a *competitive antagonist*. There are two general types of antagonists, competitive antagonists and noncompetitive antagonists. The former, which is the larger category, is one in which the degree of antagonism is dependent on the relative concentrations of the agonist and the antagonist; both bind to the same site on the receptor, or, at least, the antagonist directly interferes with the binding of the agonist. The degree of blocking of a *noncompetitive antagonist* (Y′) is independent of the amount of agonist present; two different binding sites may be involved (Fig. 3.10C). Only competitive antagonists will be discussed further in this text.

If a compound Z is added to the tissue preparation and some response is elicited, but not a full response, regardless of how high the concentration of Z used, then Z is called a *partial agonist* (see Fig. 3.11A). A partial agonist has properties of both an agonist and an antagonist. When Z is added to low concentrations of a neurotransmitter sufficient to give a response less than the maximal response of the partial agonist (e.g., 20% as shown in Fig. 3.11B), additive effects are observed as Z is increased, but the maximum response

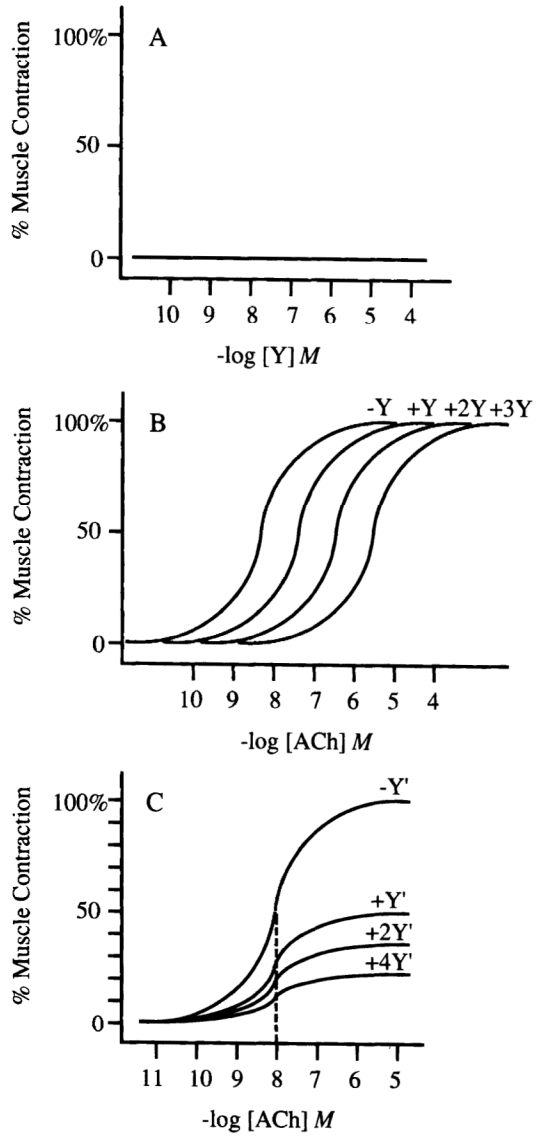


Figure 3.10. (A) Dose–response curve for an antagonist; (B) effect of a competitive antagonist (Y) on the response of a neurotransmitter; and (C) effect of a noncompetitive antagonist (Y′) on the response of the neurotransmitter.

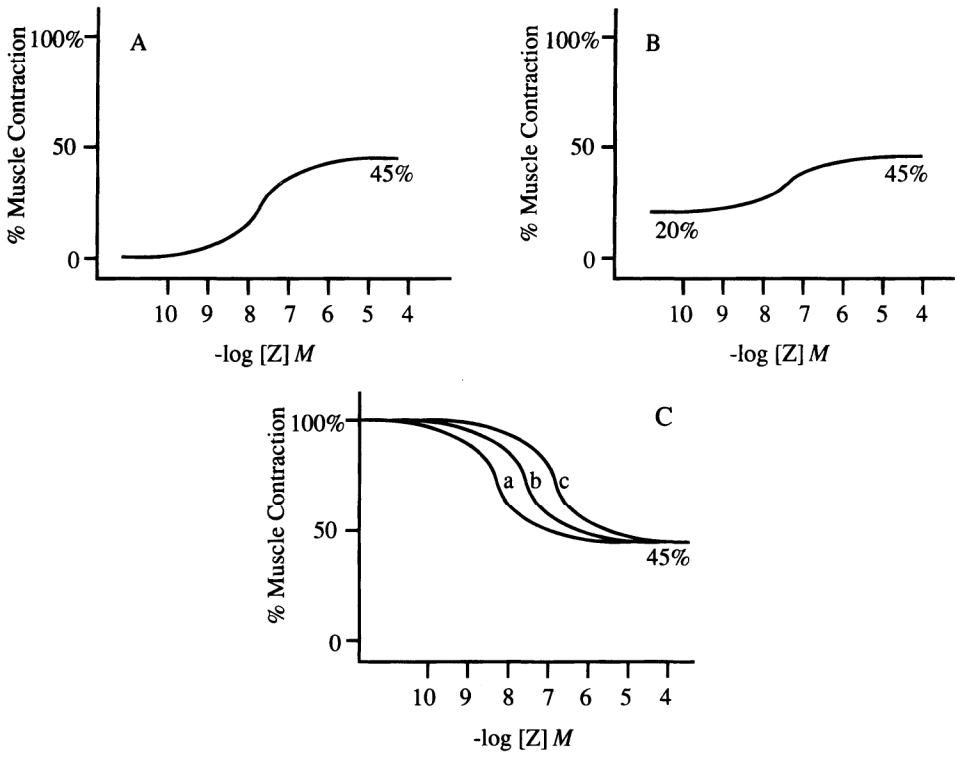


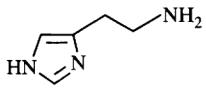
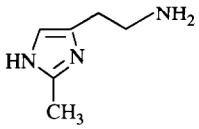
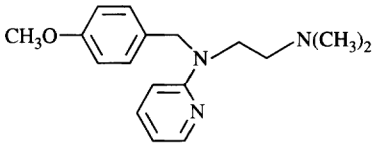
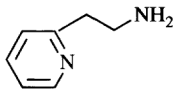
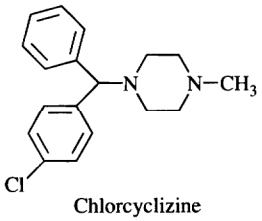
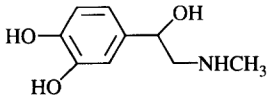
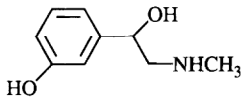
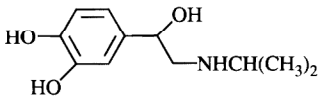
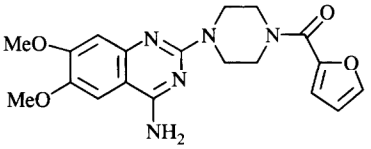
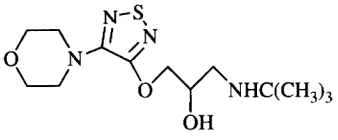
Figure 3.11. (A) Dose–response curve for a partial agonist; (B) effect of a low concentration of neurotransmitter on the response of a partial agonist; and (C) effect of a high concentration of neurotransmitter on the response of a partial agonist. In (C) the concentration of the neurotransmitter is c > b > a.

does not exceed that produced by Z alone. Under these conditions, the partial agonist is having an agonistic effect. However, if Z is added to high concentrations of a neurotransmitter sufficient to give full response of the neurotransmitter, then antagonistic effects are observed; as Z increases, the response decreases to the point of maximum response of the partial agonist (Fig. 3.11C). If this same experiment is done starting with higher concentrations of the neurotransmitter, the same results are obtained except that the dose–response curves shift to the right, resembling the situation of adding an antagonist to the neurotransmitter.

On the basis of the above discussion, if you wish to design a drug to effect a certain response, an agonist would be desired; if you wish to design a drug to prevent a particular response of a neurotransmitter or hormone, an antagonist would be required.

In general, there are great structural similarities among a series of agonists, but little structural similarity exists in a series of competitive antagonists. For example, Table 3.1 shows some agonists and antagonists for histamine and epinephrine; a more detailed list of agonists and antagonists for specific receptors has been reported.[18] The differences in the structures of the antagonists are not surprising because a receptor can be blocked by an antagonist simply by its binding to a site near enough to the binding site for the neurotransmitter that it physically blocks the neurotransmitter from reaching its binding site.

Table 3.1 Agonists and Antagonists

Neurotransmitter	Agonists	Antagonists
 Histamine		 Pyrilamine
		 Chlorcyclizine
 Epinephrine	 	 Prazosin  Timolol

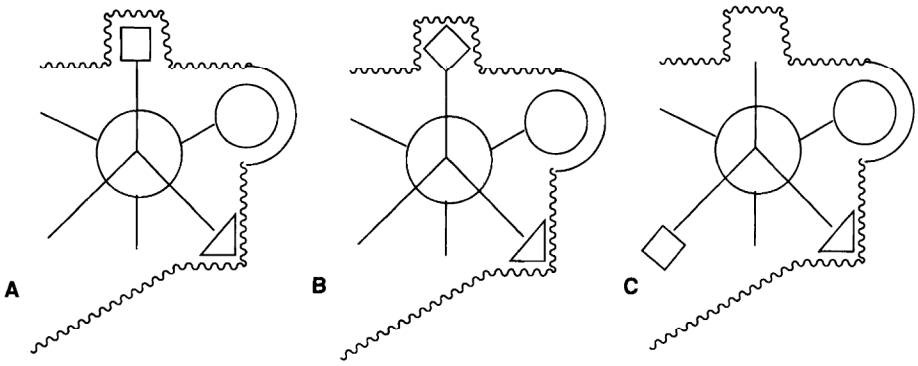


Figure 3.12. Inability of an antagonist to elicit a biological response. The wavy line is the receptor surface. (Adapted with permission from W. O. Foye, ed. 1989 "Principles of Medicinal Chemistry," 3rd Ed., p. 63. Copyright © 1989 Lea & Febiger, Philadelphia, Pennsylvania.)

This may explain why antagonists are frequently much more bulky than the corresponding agonists. It is easier to design a molecule that blocks a receptor site than one that interacts with it in the specific way required to elicit a response. An agonist can be transformed into an antagonist by appropriate structural modifications (see Section III,H).

How is it possible for an antagonist to bind to the same site as an agonist and not elicit a biological response? There are several ways that this may occur. Figure 3.12A shows an agonist with appropriate groups interacting with three receptor binding sites and eliciting a response. In Fig. 3.12B the compound has two groups that can interact with the receptor, but one essential group is missing. In the case of optical isomers (Fig. 3.12C), only two groups are able to interact with the proper receptor sites. If appropriate groups must interact with all three binding sites in order for a response to be elicited, then the compounds depicted in Fig. 3.12B and C would be antagonists.

There are two general categories of compounds that interact with receptors: (1) compounds that occur naturally within the body, such as hormones, neurotransmitters, and other agents that modify cellular activity (*autocoids*), and (2) *xenobiotics*, compounds that are foreign to the body. All chemicals naturally occurring in the body are known to act as agonists, but most xenobiotics that interact with receptors are antagonists.

Receptor selectivity is very important but often difficult to attain because receptor structures are generally unknown. Many current drugs are pharmacologically active at multiple receptors, some of which are not associated with the illness that is being treated. This can lead to side effects. For example, the clinical effect of neuroleptics is believed to result from their antagonism of dopamine receptors.[19] In general, this class of drugs also blocks cholinergic and α-adrenergic receptors, and this results in side effects such as sedation and hypotension.

E. Drug–Receptor Theories

Over the years a number of theories have been proposed to account for the ability of a drug to interact with a receptor and elicit a biological response. Several of the more important suggestions are discussed here.

1. Occupancy Theory

The *occupancy theory* of Gaddum[20] and Clark[21] states that the intensity of the pharmacological effect is directly proportional to the number of receptors occupied by the drug. The response ceases when the drug–receptor complex dissociates. However, as discussed in Section III,D, not all agonists produce a maximal response. Therefore, this theory does not rationalize partial agonists.

Ariëns[22] and Stephenson[23] modified the occupancy theory to account for partial agonists, a term coined by Stephenson. These authors utilized the original Langley[3] concept of a receptor that drug–receptor interactions involve two stages: first, there is a complexation of the drug with the receptor, which they both termed the *affinity*; second, there is the initiation of the biological effect which Ariëns termed the *intrinsic activity* and Stephenson called the *efficacy*. Affinity, then, is a measure of the capacity of a drug to bind to the receptor and is dependent on the molecular complementarity of the drug and the receptor. Intrinsic activity (α) is a measure of the ability of the drug–receptor complex to initiate the response. In the original theory the latter property was considered to be constant. Examples of affinity and intrinsic activity are given in Fig. 3.13. Figure 3.13A shows the theoretical dose–response curves for five drugs with the same affinity for the receptor (pK_D = 8) but having intrinsic activities varying from 100% of the maximum (α = 1.0)

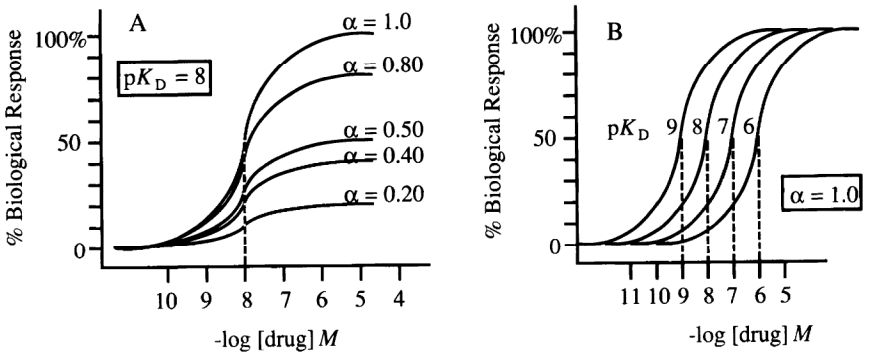


Figure 3.13. Theoretical dose–response curves to illustrate (A) drugs with equal affinities and different intrinsic activities and (B) drugs with equal intrinsic activities but different affinities.

to 20% of the maximum (α = 0.20). The drug with α equal to 1.0 is a full agonist; the ones with α less than 1.0 are partial agonists. Figure 3.13B shows the dose–response curves for four drugs with the same intrinsic activity (α = 1.0) but having different affinities varying from a pK_D of 9 to 6.

In general, antagonists bind tightly to a receptor (great affinity) but are devoid of activity (no efficacy). Potent agonists may have less affinity for their receptors than partial agonists or antagonists. The modified occupancy theory accounts for the existence of partial agonists and antagonists, but it does not account for why two drugs that can occupy the same receptor can act differently, namely, one as an agonist, the other as an antagonist.

2. Rate Theory

As an alternative to the occupancy theory, Paton[24] proposed that the activation of receptors is proportional to the total number of encounters of the drug with its receptor per unit time. Therefore, the *rate theory* suggests that the pharmacological activity is a function of the rate of association and dissociation of the drug with the receptor, and not the number of occupied receptors. Each association would produce a quantum of stimulus. In the case of agonists, the rates of both association and dissociation would be fast (the latter faster than the former). The rate of association of an antagonist with a receptor would be fast, but the dissociation would be slow. Partial agonists would have intermediate drug–receptor complex dissociation rates. At equilibrium, the occupancy and rate theories are mathematically equivalent. As in the case of the occupancy theory, the rate theory does not rationalize why the different types of compounds exhibit the characteristics that they do.

3. Induced-Fit Theory

The *induced-fit theory* of Koshland[25a–c] was originally proposed for the action of substrates and enzymes, but it could apply to drug–receptor interactions as well. According to this theory the receptor (enzyme) need not necessarily exist in the appropriate conformation required to bind the drug (substrate). As the drug (substrate) approaches the receptor (enzyme), a conformational change is induced which orients the essential binding (catalytic) sites (Fig. 3.14). The conformational change in the receptor could be responsible for the initiation of the biological response. The receptor (enzyme) was suggested to be elastic, and it could return to its original conformation after the drug (substrate) was released. The conformational change need not occur only in the receptor (enzyme); the drug (substrate) also could undergo deformation, even if this resulted in strain in the drug (substrate).

According to the induced-fit theory, an agonist would induce a conformational change and elicit a response, but an antagonist would bind without a

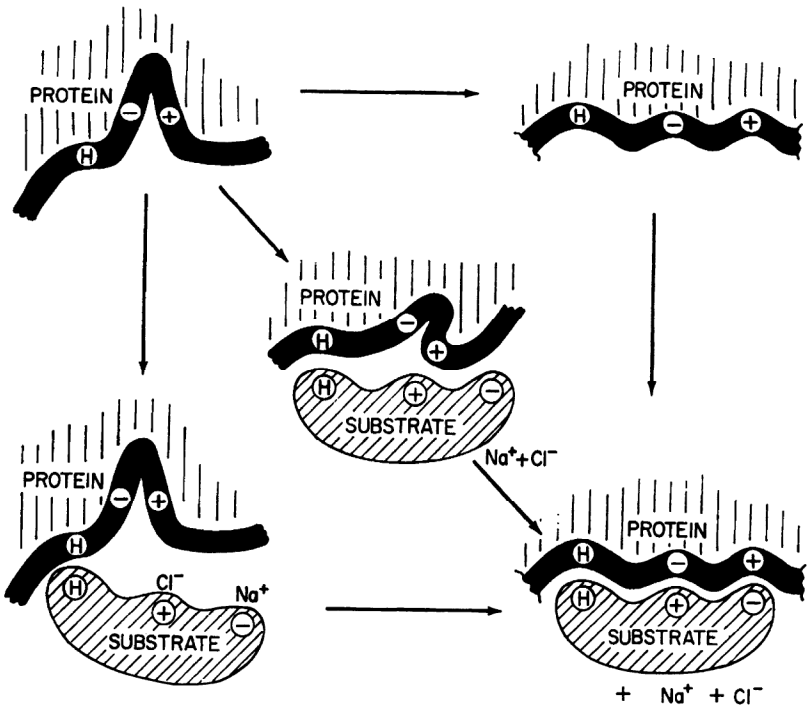


Figure 3.14. Schematic of the induced-fit theory. [Reproduced with permission from Koshland, Jr., D. E., and Neet K. E., Annual Review of Biochemistry, Vol. 37, © 1968 by Annual Reviews, Inc.]

conformational change. This theory also can be adapted to the rate theory. An agonist would induce a conformational change in the receptor, resulting in a conformation to which the agonist binds less tightly and from which it can dissociate more easily. If drug–receptor complexation does not cause a conformational change in the receptor, then the drug–receptor complex will be stable, and an antagonist will result. Two other theories evolved from the induced-fit theory, namely, the macromolecular perturbation theory and the activation–aggregation theory.

4. Macromolecular Perturbation Theory

Having considered the conformational flexibility of receptors, Belleau[26] suggested that in the interaction of a drug with a receptor two general types of *macromolecular perturbations* could result: *specific conformational perturbation* makes possible the binding of certain molecules that produce a biological response (agonist); *nonspecific conformational perturbation* accommodates other types of molecules that do not elicit a response (antagonist). If the

drug contributes to both macromolecular perturbations, a mixture of two complexes will result (partial agonist). This theory offers a physicochemical basis for the rationalization of molecular phenomena that involve receptors.

5. Activation–Aggregation Theory

An extension of the macromolecular perturbation theory (which is based on the induced-fit theory) is the *activation–aggregation theory* of Changeux and co-workers[27] and Karlin.[28] According to this theory, even in the absence of drugs, a receptor is in a state of dynamic equilibrium between an activated form (R_o), which is responsible for the biological response, and an inactive form (T_o). Agonists shift the equilibrium to the activated form, antagonists bind to the inactive form, and partial agonists bind to both conformations. In this model the agonist binding site in the R_o conformation can be different from the antagonist binding site in the T_o conformation. If there are two different binding sites and conformations, then this could account for the structural differences in these classes of compounds and could rationalize why an agonist elicits a biological response but an antagonist does not. This theory can explain the ability of partial agonists to possess both the agonistic and antagonistic properties as depicted in Fig. 3.11. In Fig. 3.11B as the partial agonist interacts with the remaining unoccupied receptors, there is an increase in the response up to the maximal response for the partial agonist interaction. In Fig. 3.11C the partial agonist competes with the neurotransmitter for the receptor sites. As the partial agonist displaces the neurotransmitter, it changes the amount of R_o and T_o receptor forms (T_o increases and, therefore, the response decreases) until all of the receptors have the partial agonist bound.

It is generally accepted in the field of enzymology that conformational changes are quite important to enzyme function. Although noncatalytic receptors are far less characterized, it is reasonable to extrapolate what is known about enzymes to all types of receptors and to assume an important role for conformational changes in drug–receptor interactions in general.

F. Topographical and Stereochemical Considerations

Up to this point in our discussion of drug–receptor interactions we have been concerned with what stabilizes a drug–receptor complex, how drug–receptor interactions are measured, and possible ways that the drug–receptor complex may form. In this section we turn our attention to molecular aspects and examine the topography and stereochemistry of drug–receptor complexes.

1. Spatial Arrangement of Atoms

It was indicated in the discussion of bioisosterism (Chapter 2, Section II,D,4) that many antihistamines have a common structural feature (Fig. 3.15).[29] In Fig. 3.15 Ar^1 is aryl, such as phenyl, substituted phenyl, or heteroaryl (2-pyridyl or thienyl); Ar^2 is aryl or arylmethyl. The two aryl groups also can be connected through a bridge (as in phenothiazines, **2.34**), and the CH_2CH_2N moiety can be part of another ring (as in chlorcyclizine, Table 3.1). X is CH—O—, N—, or CH—; C—C is a short carbon chain (2 or 3 atoms) which may be saturated, branched, contain a double bond, or be part of a ring system. These compounds are called antihistamines because they are antagonists of a histamine receptor known as the *H_1 receptor*. When a sensitized person is exposed to an allergen, an antibody is produced, an antigen–antibody reaction occurs, and histamine is released. Histamine binding to the H_1 receptor can cause stimulation of smooth muscle and produce allergic and hypersensitivity reactions such as hay fever, pruritus (itching), contact and atopic dermatitis, drug rashes, urticaria (edematous patches of skin), and anaphylactic shock. Antihistamines are used widely to treat these symptoms. Unlike histamine (see Table 3.1 for structure), most H_1 blockers contain tertiary amino groups, usually dimethylamino or pyrrolidino. At physiological pH, then, this group will be protonated, and it is believed that an ionic interaction with the receptor is a key binding contributor.

The commonality of structures of antihistamines suggests that there are specific binding sites on the histamine H_1 receptor that have an appropriate topography for interaction with certain groups on the antihistamine which are arranged in a similar configuration (see Section III,B). Those parts of the drug molecule that interact with the receptor are known as the *pharmacophore* of the compound; this is the key interaction that is responsible for the biological response. It must be cautioned, however, that although the antihistamines are competitive antagonists of histamine for the H_1 receptor, the same set of atoms on the receptor need not interact with both histamine and the antagonists.[30] Consequently, it is difficult to make conclusions regarding the receptor structure on the basis of antihistamine structure–activity relationships. Because of the essentiality of various parts of antihistamine molecules, it is likely that the minimum binding requirements include a negative charge on the receptor to interact with the ammonium cation and hydrophobic (van der

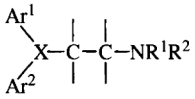


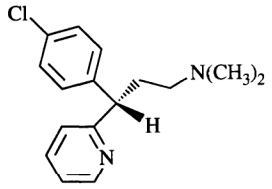
Figure 3.15. General structure of antihistamines.

Waals) interactions with the aryl group. Obviously, many other interactions are involved.

From this very simplistic view of drug–receptor interactions it is not possible to rationalize the fact that enantiomers, that is, mirror image compounds that are identical in all physical and chemical properties except for their effect on the direction of rotation of the plane of polarized light, can have quite different binding properties to receptors. This phenomenon is discussed in more detail in the next section.

2. Drug and Receptor Chirality

Histamine is an achiral molecule, and most of the H_1 receptor antagonists are achiral molecules as well. However, proteins are polyamino acid macromolecules, and amino acids are chiral molecules (in the case of mammalian proteins, they are all L-isomers); consequently, proteins (receptors) are chiral substances. The two complexes formed between a receptor and two enantiomers are diastereomers and, as a result, have different energies and chemical properties. This suggests that dissociation constants for drug–receptor complexes of enantiomeric drugs may differ, and may even involve different binding sites. Even though histamine is achiral, the chiral antihistamine dexchlorpheniramine (**3.12**) is highly *stereoselective* (one stereoisomer is more active than the other); the (*S*)-(+)-isomer is about 200 times more potent than the (*R*)-(−)-isomer.[31] According to the nomenclature of Ariëns,[32a,b] when there is isomeric stereoselectivity, the more active isomer is termed the *eutomer*; the less active isomer is the *distomer*. The ratio of the potencies (or affinities) of enantiomers is termed the *eudismic ratio*.

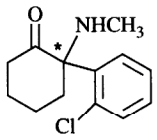


***S*-(+)-3.12**

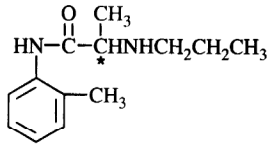
High-potency antagonists are those having a high degree of complementarity with the receptor. When the antagonist contains an asymmetric center in the pharmacophore, a high eudismic ratio is usually observed for the stereoisomers because the receptor complementarity would not be retained for the distomer. This increase in eudismic ratio with an increase in potency of the eutomer is *Pfeiffer's rule*.[32b,33] Small eudismic ratios are observed when the eutomer has low affinity for the receptor (poor molecular complementarity) or, in the case of chiral compounds, when the center of asymmetry lies

outside of the region critically involved in receptor binding, that is, the pharmacophore.

The distomer actually should be considered as an impurity in the mixture or, in the terminology of Ariëns,[32a] the *isomeric ballast*. It, however, may contribute to undesirable side effects and toxicity; in that case, the distomer for the biological activity may be the eutomer for the side effects. For example, *d*-ketamine (**3.13**; the asterisk marks the chiral carbon) is a hypnotic and analgetic agent; the *l*-isomer is responsible for the undesired side effects[34] [note that *d* is synonymous with (+) and *l* is synonymous with (−)]. It also is possible that both isomers are biologically active, but only one contributes to the toxicity, such as the local anesthetic prilocaine (**3.14**).[35]

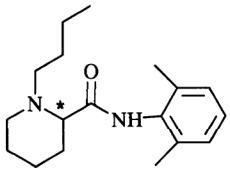


3.13

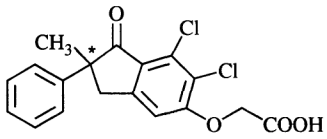


3.14

In some cases it is desirable to have both isomers present.[32] Both isomers of bupivacaine (**3.15**) are local anesthetics, but only the *l*-isomer shows vasoconstrictive activity.[36] The experimental diuretic (increases water excretion) drug indacrinone (**3.16**) has a uric acid retention side effect. The *d*-isomer of **3.16** is responsible (i.e., the eutomer) for both the diuretic activity and the side effect. Interestingly, however, the *l*-isomer acts as a uricosuric agent (reduces uric acid levels). Unfortunately, the ratio that gives the optimal therapeutic index (see Chapter 2, Section II,D) is 1*d*:8*l*, not 1:1 as is present in the racemic mixture.[37]

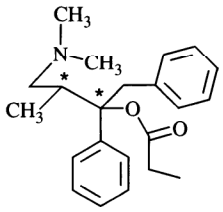


3.15

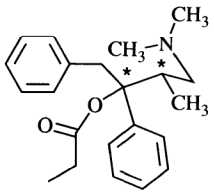


3.16

Enantiomers may have different therapeutic activities as well.[38] Darvon® (**3.17**), (2*S*,3*R*)[38a]-(+)-dextropropoxyphene, is an analgetic drug, and its enantiomer Novrad® (**3.18**), (−)-levopropoxyphene, is an antitussive (anticough) agent, an activity that is not compatible with analgetic action. Consequently, these enantiomers are marketed separately. You may have noticed that the trade names are enantiomeric as well!

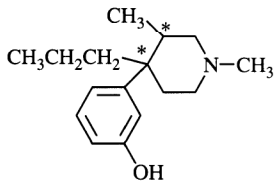


3.17



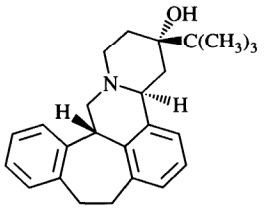
3.18

It, also, is possible for the enantiomers to have opposite effects. The *l*-isomers of some barbiturates exhibit depressant activity and the *d*-isomers have convulsant activity; the *l*-isomers can antagonize the *d*-isomers.[39] The *d*-isomer of the experimental narcotic analgetic picenadol (**3.19**) is an opiate agonist, the *l*-isomer is a narcotic antagonist, and the racemate is a partial agonist.[40]

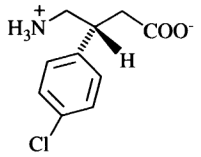


3.19

It is quite common for chiral compounds to show stereoselectivity with receptor action, and the stereoselectivity of one compound can vary for different receptors. For example, (+)-butaclamol (**3.20**) is a potent antipsychotic, but the (−)-isomer is essentially inactive; the eudismic ratio (+/−) is 1250 for the D_2-dopaminergic, 160 for the D_1-dopaminergic, and 73 for the α-adrenergic receptors.[32b] (−)-Baclofen (**3.21**) is a muscle relaxant that binds to the γ-aminobutyric acid-B ($GABA_B$) receptor; the eudismic ratio (−/+) is 800.[41]



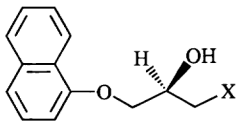
(+)-3.20



(-)-3.21

It should be remembered that the (+) and (−) nomenclature refers to the effect of the compound on the direction of rotation of the plane of polarized light, and it has nothing to do with the stereochemical configuration of the molecule. The stereochemistry about a chiral carbon atom is noted by the

(*R*,*S*) convention of Cahn *et al.*[42] Since the (*R*,*S*) convention is determined by the atomic numbers of the substituents about the chiral center, two compounds having the same stereochemistry, but a different substituent can have opposite chiral nomenclatures. For example, the eutomer of the antihypertensive agent propranolol is the (*S*)-(−)-isomer [**3.22**, X = $NHCH(CH_3)_2$].[43] If X is varied so that the attached atom has an atomic number greater than that of oxygen, such as F, Cl, Br, or SR, then the nomenclature rules[42] dictate that the molecule is designated as an (*R*)-isomer, even though there is no change in the stereochemistry. Note, however, that even though the absolute configuration about the chiral carbon remains unchanged after variation of the X group in **3.22**, the effect on plane polarized light cannot necessarily be predicted; the compound with a different substituent X can be either + or −. The most common examples of this phenomenon in nature are some of the amino acids. (*S*)-Alanine, for example, is the (+)-isomer and (*S*)-serine (same absolute stereochemistry) is the (−)-isomer; the only difference is a CH_3 group for alanine and a CH_2OH group for serine.



(-)-3.22

Propranolol [**3.22**, X = $NHCH(CH_3)_2$] is an antagonist of the β-adrenergic receptor, which triggers vasodilation; the β_1- and β_2-adrenergic receptors are important to cardiac and bronchial vasodilation, respectively. The eudismic ratio (*l*/*d*) for propranolol is about 100; however, propranolol also exhibits local anesthetic activity for which the eudesmic ratio is 1. The latter activity apparently is derived from some other mechanism than β-adrenergic blockage. A compound of this type that has two separate mechanisms of action and, therefore, different therapeutic activities, has been called a *hybrid drug* by Ariëns.[44] (+)-Butaclamol (**3.20**), which interacts with a variety of receptors, is another hybrid drug. However, butaclamol has three chiral centers and, therefore, has eight possible isomeric forms. When multiple isomeric forms are involved in the biological activity, the drug is called a *pseudo hybrid drug*.[44] Another important example of this type of drug is the antihypertensive agent, labetalol (Fig. 3.16), which, as a result of two asymmetric carbon atoms, exists in four stereoisomeric forms, having the stereochemistries (*RR*), (*SS*), (*RS*), and (*SR*). This drug has α- and β-adrenergic blocking properties. The (*RR*)-isomer is predominantly the β-blocker (the eutomer for β-adrenergic blocking action), and the (*SR*)-isomer is mostly the α-blocker (the eutomer for α-adrenergic blocking); the other 50% of the isomers, the (*SS*)- and (*RS*)-isomers, are almost inactive (the isomeric ballast). Labetalol,

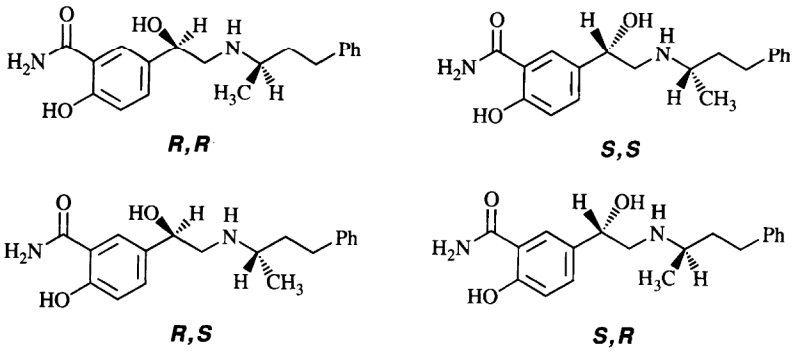
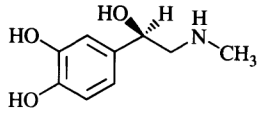


Figure 3.16. Four stereoisomers of labetalol.

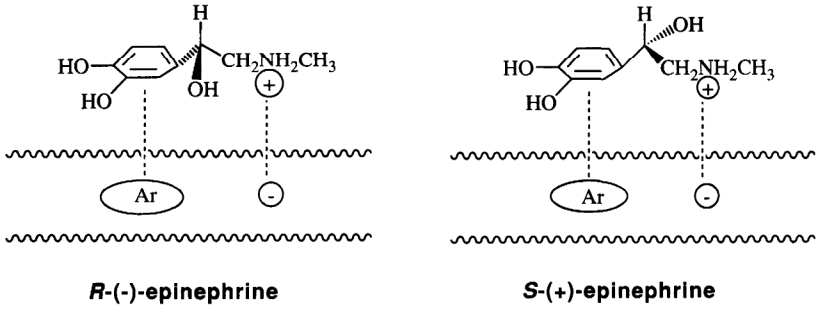
then, is a pseudo hybrid, a mixture of isomers having different receptor-binding properties.

Labetalol also is an example of how relatively minor structural modifications of an agonist can lead to transformation into an antagonist. *l*-Epinephrine (**3.23**) is a natural hybrid molecule that induces both α- and β-adrenergic effects. Introduction of the phenylalkyl substituent on the nitrogen transforms the α-adrenergic activity of the agonist *l*-epinephrine into the α-adrenergic antagonist labetalol. The modification of one of the catechol hydroxyl groups of *l*-epinephrine to a carbamyl group of labetalol changes the β-adrenergic action (agonist) to a β-adrenergic blocking action (antagonist).



3.23

As pointed out by Ariëns[32a,b,44] and by Simonyi,[45] it is quite common for mixtures of isomers, particularly racemates, to be marketed as a single drug, even though at least half of the mixture not only may be inactive for the desired biological activity, but may, in fact, be responsible for various side effects. In the case of β-adrenergic blockers, antiepileptics, and oral anticoagulants, about 90% of the drugs on the market are racemic mixtures, and for antihistamines, anticholinergics, and local anesthetics about 50% are racemic. In general, about 25% of drugs are sold as racemic mixtures.[45] The isomeric ballast, typically, is not removed for economic reasons; it can be quite expensive to separate the enantiomeric impurity. Keep in mind, however, that because of vast differences in activities of two enantiomers, caution should be used when applying QSAR methods such as Hansch analyses (see Section



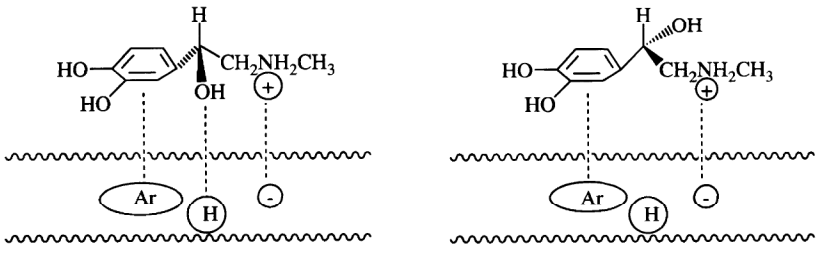
***R*-(-)-epinephrine** ***S*-(+)-epinephrine**

Figure 3.17. Binding of epinephrine enantiomers to a two-site receptor. The wavy lines are the receptor surfaces.

II,E,3,a of Chapter 2) to racemic mixtures. These methods really should be applied to the separate isomers.[46]

It is quite apparent from the above discussion that receptors are capable of recognizing and selectively binding optical isomers. Cushny[47] was the first to suggest that enantiomers could have different biological activities because one isomer could fit into a receptor much better than the other. How are they able to accomplish this?

If you consider two enantiomers, such as (*R*)-(−)- and (*S*)-(+)-epinephrine, interacting with a receptor that has only two binding sites (Fig. 3.17), it becomes apparent that the receptor cannot distinguish between them. However, if there are at least three binding sites (Fig. 3.18), the receptor easily can differentiate them. The (*R*)-(−)-isomer has three points of interaction and is held in the conformation shown to maximize molecular complementarity. The (*S*)-(+)-isomer can have only two sites of interaction (the hydroxyl group cannot interact with the hydroxyl binding site, and may even have an adverse steric interaction); consequently it has a lower binding energy. Easson and



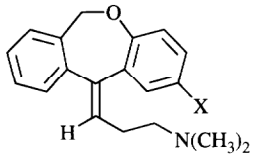
***R*-(-)-epinephrine** ***S*-(+)-epinephrine**

Figure 3.18. Binding of epinephrine enantiomers to a three-site receptor. The wavy lines are the receptor surfaces.

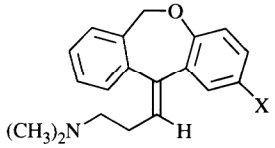
Stedman[48] were the first to recognize this "*three-point attachment*" concept: a receptor can differentiate enantiomers if there are as few as three binding sites. As in the case of the β-adrenergic receptors discussed above, the structure of α-adrenergic receptors to which epinephrine binds is unknown. α-Adrenergic receptors appear to mediate vasoconstrictive effects of catecholamines in bronchial, intestinal, and uterine smooth muscle. The eudismic ratio (R/S) for vasoconstrictor activity of epinephrine is only 12–20,[49a] indicating that there is relatively little difference in binding energy for the two isomers to the α-adrenergic receptor. Although the above discussion was directed at the enantioselectivity of receptor interactions, it should be noted that there also is enantioselectivity with respect to pharmacokinetics, namely, absorption, distribution, metabolism, and excretion.[49b]

3. Geometric Isomers

Geometric isomers (*E*- and *Z*-isomers[50] and epimers) are diastereomers, stereoisomers having different spatial arrangements of atoms; consequently, they are different compounds. As a result of their different configurations, receptor interactions will be different. For example, the antipsychotic activity of a series of *Z*-2-substituted doxepin analogs (**3.24a**) was found to be significantly greater than the corresponding *E*-isomers (**3.24b**).[51] Likewise, the neuroleptic potency of the *Z*-isomer of the antipsychotic drug chlorprothixene (**3.25a**) is more than 12 times greater than that of the corresponding *E*-isomer (**3.25b**).[51] On the other hand, the *E*-isomer of the anticancer drug diethylstilbestrol (**3.26a**) has 14 times greater estrogenic activity than the *Z*-isomer (**3.26b**), possibly because its overall structure and the interatomic distance between the two hydroxyls in the *E*-isomer are similar to that of estradiol (**3.27**).



3.24a



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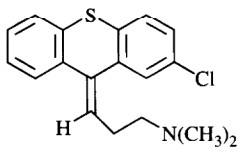
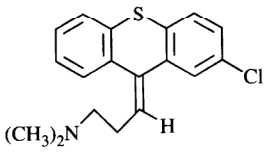
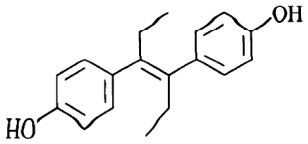


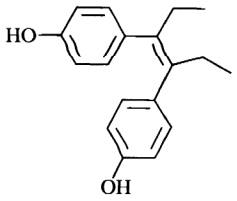
3.25a



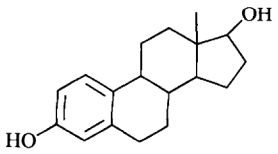
3.25b



3.26a



3.26b



3.27

Although in some cases the cis and trans nomenclature does correspond with *Z* and *E*, respectively, it should be kept in mind that these terminologies are based on different conventions,[50] so there may be confusion. The *Z*,*E* nomenclature is unambiguous and should be used.

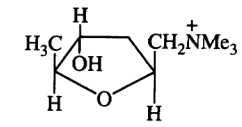
4. Conformational Isomers

As a result of free rotation about single bonds in acyclic molecules and conformational flexibility in many cyclic compounds, a drug molecule can assume a variety of *conformations*, namely, locations of the atoms in space. The pharmacophore of a molecule is defined not only by the configuration of a set of atoms, but also by their conformation in relation to the receptor binding site. A receptor may bind only one of these *conformers* (isomers generated by a change in conformation); the conformer that binds need not necessarily be the lowest energy conformer observed in the crystalline state, as determined by X-ray crystallography, or found in solution, as determined by nuclear magnetic resonance (NMR) spectrometry, or determined theoretically by molecular mechanics calculation. The binding energy to the receptor may overcome the barrier to the formation of an unstable conformer. As was pointed out in Section II,F of Chapter 2, the assumption that a drug–receptor interaction involves the lowest energy conformer is an important problem in much of molecular graphics drug design. In order for drug design to be efficient, it is essential to know the active conformation in the drug–receptor complex. If the lead compound has low potency, it may only be because the population of the active conformer in solution is low (higher in energy).

A unique approach has been taken to determine, with some degree of certainty, the active conformation of a drug molecule in the drug–receptor complex. This approach involves the synthesis of *conformationally rigid analogs* of flexible drug molecules. The potential pharmacophore becomes locked into various configurations by judicious incorporation of cyclic or unsaturated moieties into the drug molecule. The conformationally rigid analogs are, then, tested, and the analog with the optimal activity (or potency) can be used as the prototype for further structural modification. Conformationally rigid analogs are propitious because key functional groups, presumably part of the pharma-

cophore, are constrained in one position, thereby permitting the determination of the *pharmacophoric conformation*. The major drawback to this approach is that in order to construct a rigid analog of a flexible molecule, additional atoms and/or bonds must be attached to the original compound, and these can affect the chemical and physical properties. Consequently, it is imperative that the conformationally rigid analog and the drug molecule be as similar as possible in size, shape, and molecular weight.

An example of the use of conformationally rigid analogs for the elucidation of receptor binding site topography is the studies of the interaction of the neurotransmitter acetylcholine (ACh) with the muscarinic receptor. There are at least two important receptors for ACh, one activated by the alkaloid muscarine (**3.28**) and the other by the alkaloid nicotine (**3.29**; presumably in the protonated pyrrolidine form). Acetylcholine has a myriad of conformations; four of the more stable possible conformers (group staggered) are **3.30a–3.30d**. There are also conformers with groups eclipsed that are higher in energy. Four different *trans*-decalin stereoisomers were synthesized[52] (**3.31a–3.31d**) corresponding to the four ACh conformers shown in **3.30a–3.30d**. All four isomers exhibited low muscarinic receptor activity; however, **3.31a** was the most potent (0.06 times the potency of ACh). The low potency of **3.31a** is believed to be the result of the unfavorable steric effect of the *trans*-decalin moiety.[52]



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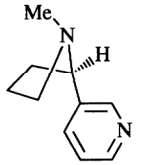

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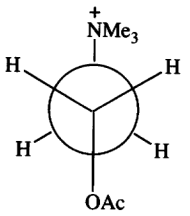
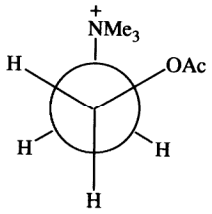
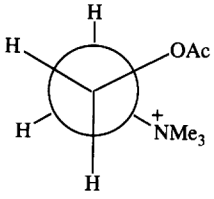


3.30a



3.30b



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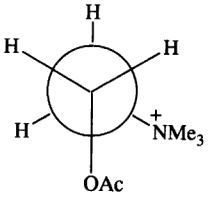
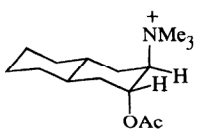
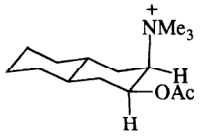


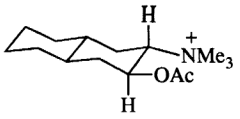
3.30d



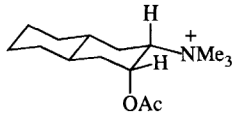
3.31a



3.31b

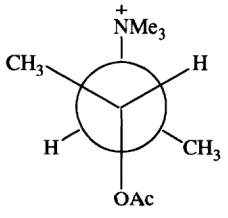


3.31c



3.31d

A comparison of *erythro*- (**3.32**) and *threo*-2,3-dimethylacetylcholine (**3.33**) gave the startling result that **3.32** was 14 times more potent than ACh and **3.33** was 0.036 times as potent as ACh. Compound **3.31a** corresponds to the threo isomer **3.33** and, therefore, is expected to have low potency. The corresponding erythro analog does not have a *trans*-decalin analogy, so it could not be tested. To minimize the number of extra atoms added to ACh, *trans*- (**3.34**) and *cis*-1-acetoxy-2-trimethylammoniocyclopropanes (**3.35**) were synthesized and tested[53] for *cholinomimetic properties*, that is, production of a response resembling that of ACh. The (+)-trans isomer (shown in **3.34**)[54] has about the same muscarinic activity as does ACh, thus indicating the importance of minimizing additional atoms; the (−)-trans isomer has about 1/500th the potency of ACh. The racemic cis isomer has negligible activity. The (+)-trans isomer was shown to have the same absolute configuration as the active enantiomers of the two muscarinic receptor agonists muscarine and acetyl β-methylcholine.[54] These results suggest that ACh binds in an extended form (**3.30a**). Both the cis and the trans isomers, as well as all of the *trans*-decalin stereoisomers (**3.31a–3.31d**) were weakly active with the nicotinic cholinergic receptor.



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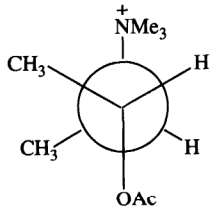

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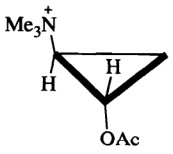

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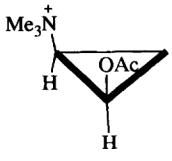
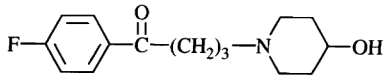


3.35

An example of the use of conformationally rigid analogs in drug design was reported by Li and Biel.[55] 4-(4-Hydroxypiperidino)-4′-fluorobutyrophenone (**3.36**) was found to have moderate tranquilizing activity in lower animals and man; however, unlike the majority of antipsychotic butyrophenone-type

compounds, it only has minimal antiemetic (prevents vomiting) activity. The piperidino ring can exist in various conformations [**3.37a–3.37d**, R = F—$C_6H_4CO(CH_2)_3$—], two chair forms (**3.37a** and **3.37d**) and two twist–boat forms (**3.37b** and **3.37c**). The difference in free energy between the axial and equatorial hydroxy conformers of the related compound *N*-methyl-4-piperidinol (**3.37**, R = Me) is 0.94 ± 0.05 kcal/mol at 40°C (the equatorial conformer is favored by a factor of 4.56 over the axial conformers).[56] Energies for the twist–boat conformers are about 6 kcal/mol higher, but because of hydrogen bonding, **3.37b** should be more stable than **3.37c**. On the assumption that the chair conformers are more likely, three conformationally rigid chair analogs, **3.38–3.40**, were synthesized to determine the effect on receptor binding of the hydroxyl in the equatorial (**3.38**), axial (**3.39**), and both (**3.40**) positions. Of course, there will be no hydroxyl group hydrogen-bonding effects with **3.40**. When subjected to muscle relaxation tests, the order of potency was **3.39** > **3.40** > **3.38**, indicating that the conformationally less stable compound with the axial hydroxyl group has better molecular complementarity with the receptor than does the more stable compound with the equatorial hydroxyl group. This suggests that future analogs should be prepared where the axial hydroxyl is the more stable conformer or where it can be held in that configuration.



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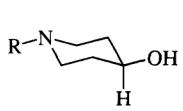

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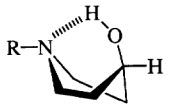
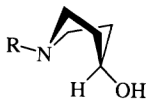
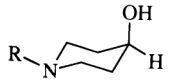


3.37b



3.37c



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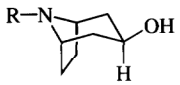

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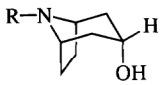

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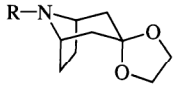


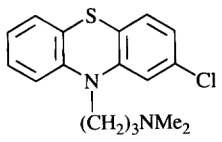
3.40

Another use of conformationally rigid analogs is to prepare compounds that have conformational features common to potent analogs which cannot be adopted by inactive analogs. This is the strategy of drug design that can be used in conjunction with the molecular graphics approach known as steric mapping (see Section II,F of Chapter 2).

5. Ring Topology

Tricyclic psychomimetic drugs show an almost continuous transition of activity in going from structures such as the tranquilizer chlorpromazine (**3.41**)

through the antidepressant amitriptyline (**3.42**), which has a tranquilizing side effect, to the pure antidepressant agent imipramine (**3.43**).[57] Stereoelectronic effects seem to be the key factor, even though tranquilizers and antidepressants have different molecular mechanisms. Three angles can be drawn to define the positions of the two aromatic rings in these compounds (Fig. 3.19). The angle α (**3.44**) describes the bending of the ring planes; β (**3.45**) is the annellation angle of the ring axes that pass through carbon 1 and 4 of each aromatic ring; γ (**3.46**) is the torsional angle of the aromatic rings as viewed from the side of the molecule. In general, the tranquilizers have only a bending angle α and no β and γ angles. The mixed tranquilizer–antidepressants have both a bending (α) and annellation angle (β), but no γ angle. The pure antidepressants exhibit all three angles.



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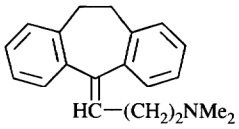

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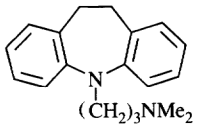
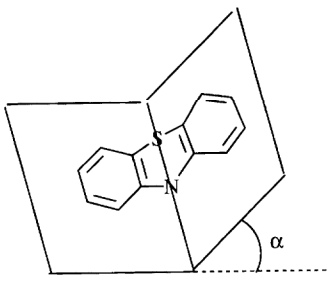


3.43

G. Ion Channel Blockers[58]

A receptor was defined in Section II,A as having two basic characteristics, recognition of a substance and ability to initiate a biological response. Ion channels, then, fulfill the definition of receptors: they selectively bind ions and they mediate a response, namely, ion transport. An *ion channel* is a transmembrane pore that is composed of three elements, a *pore* responsible



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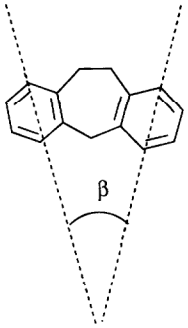

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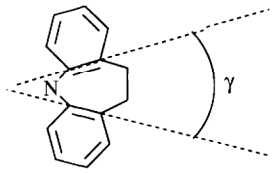
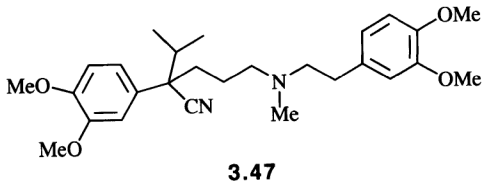


3.46

Figure 3.19. Ring topology of tricyclic psychomimetic drugs. [Reproduced with permission from Nogrady, T. (1985). *In* "Medicinal Chemistry: A Biochemical Approach," p. 29. Oxford University Press, New York. Copyright © 1985 Oxford University Press.]

for the transit of the ion and one or more *gates* that open and close in response to specific stimuli that are received by the *sensors*. Conformational mobility is an integral component of the function of ion channels; the three states of a channel, closed, open, and activated, are all believed to be regulated by conformational changes. Ligands may gain access to the channel either by membrane permeation or through an open channel state.

The movement of calcium ions into cells is vital to the excitation and contraction of the heart muscle. When a cardiac cell potential reaches a threshold, a sodium ion channel allows rapid influx of sodium ions through the cell membrane. This is followed by a slower movement of calcium ions through a calcium ion channel; the calcium ions maintain the plateau phase of the cardiac action potential. *Calcium ion channel blockers* prevent the influx of calcium ions, which then alters the plateau phase and, therefore, the coronary blood flow. Consequently, calcium channel blockers such as verapamil (**3.47**), nifedipine (**3.48**), and diltiazem (**3.49**) are valuable drugs in the treatment of angina (resulting from reduced oxygen), cardiac arrhythmias, and hypertension.



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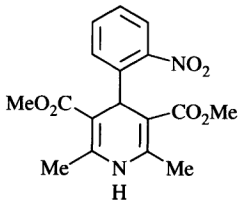

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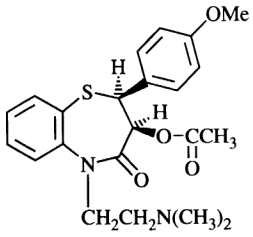
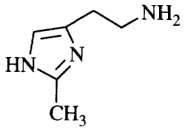


3.49

H. Example of Rational Drug Design of a Receptor Antagonist: Cimetidine

The antiulcer drug cimetidine is a truly elegant example of lead discovery and the use of physical organic chemical principles, coupled with the various lead modification approaches discussed in Chapter 2, to uncover the first histamine H_2 receptor antagonist and an entirely new class of drugs. This is a case, however, where neither QSAR nor molecular graphics approaches were utilized. As described in Section III,F,1, histamine binds to the H_1 receptor and causes allergic and hypersensitivity reactions, which antihistamines antago-

nize. It is now known that another action of histamine is the stimulation of gastric acid secretion. However, antihistamines have no effect on this activity; consequently, it was suggested that there was a second histamine receptor, which was termed the H_2 receptor. The H_1 and H_2 receptors can be differentiated by agonists and antagonists. 2-Methylhistamine (**3.50**) preferentially elicits H_1 receptor responses, and 4-methylhistamine (**3.51**) has the corresponding preferential effect on H_2 receptors. An antagonist of the histamine H_2 receptor would be beneficial to the treatment of hypersecretory conditions such as duodenal and gastric ulcers. Consequently, in 1964 Smith, Kline & French Laboratories in England initiated a search for a lead compound that would antagonize the H_2 receptor.[29,59]



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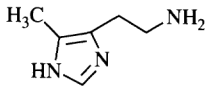
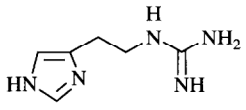


3.51

The first requirement for initiation of a lead discovery program is an efficient bioassay. Histamine was infused into anesthetized rats to stimulate gastric acid secretion, then the pH of the perfusate from the lumen of the stomach was measured before and after administration of the compound.

The lead discovery approach that was taken involved a biochemical rationale. Since a histamine receptor antagonist was sought, histamine analogs were synthesized on the assumption that the receptor would recognize that general backbone structure. However, the structure had to be sufficiently different so as not to stimulate a response and defeat the purpose. It took the group at Smith, Kline & French four years and the synthesis of about 200 compounds until the lead compound, N^{α}-guanylhistamine (**3.52**), was discovered. This compound was only very weakly active as an inhibitor of histamine stimulation; later it was determined to be a partial agonist, not an antagonist. The isosteric isothiourea (**3.53**) was found to be more active. The corresponding conformationally rigid analog **3.54** was less potent than **3.53**; consequently, it was thought that flexibility in the side chain was important. Many additional compounds were synthesized, but they acted as partial agonists. They could block histamine binding, but they could not inhibit acid secretion.



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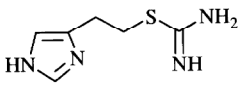

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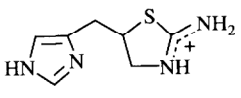
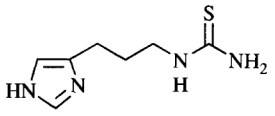


3.54

It, therefore, became necessary to separate the agonist and antagonist activities. The reason for the agonistic activity, apparently, was the structural

similarity to histamine. Not only were these compounds imidazoles, but at physiological pH the side chains were protonated and positively charged, just like histamine. Consequently, it was reasoned that the imidazole ring should be retained for receptor recognition, but the side chain could be modified to eliminate the positive charge. After numerous substitutions, a thiourea analog (**3.55**) was prepared having weak antagonistic activity without stimulatory activity. Homologation of the side chain gave a purely competitive antagonist (**3.56**, R = H); no agonist effects were observed. The *N*-methyl analog (**3.56**, R = CH_3), called burimamide, was found to be highly specific as a competitive antagonist of histamine at the H_2 receptor. It was shown to be effective in the inhibition of histamine-stimulated gastric acid secretion in rat, cat, dog, and man. Burimamide was the first H_2 receptor antagonist tested in humans, but it lacked adequate oral activity, so the search for more potent analogs was continued.



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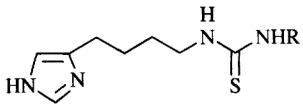
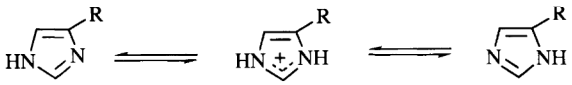


3.56

The poor oral potency of burimamide could be a pharmacokinetics problem or a pharmacodynamics problem. Let's consider the latter. In aqueous solution at physiological pH the imidazole ring can exist in three main forms (**3.57a–3.57c**, Fig. 3.20; R is the rest of burimamide). The thioureido group can exist as four conformers (**3.58a–3.58d**, Fig. 3.21; R is the remainder of burimamide). The side chain can exist in a myriad of conformations. Therefore, it is possible that only a very small fraction of the molecules in equilibrium would have the active structure, and this could account for the low potency.

One approach taken to increase the potency of burimamide was to compare the population of the imidazole form in burimamide at physiological pH to that in histamine.[60] The population can be estimated from the electronic influence of the side chain, which alters the electron densities at the ring nitrogen atoms and, therefore, affects the proton acidity. This effect is more important at the nearer nitrogen atom, so if R is electron releasing, **3.57c** (Fig. 3.20) should predominate; if R is electron withdrawing, **3.57a** should be favored.



3.57a **3.57b** **3.57c**

Figure 3.20. Three principal forms of 5-substituted imidazoles at physiological pH.

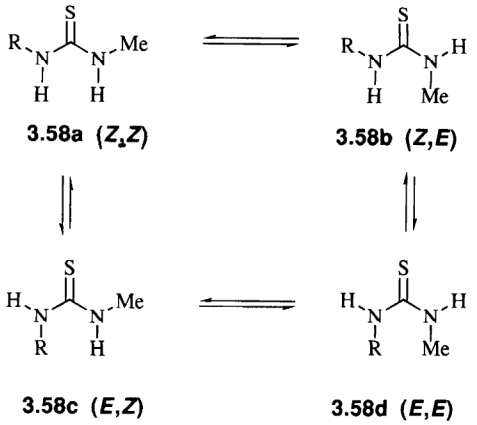


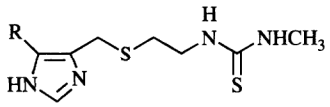
Figure 3.21. Four conformers of the thioureido group.

The fraction present as **3.57b** can be determined from the ring pK_a and the pH of the solution. The electronic effect of R can be calculated from the measured ring pK_a with the use of the Hammett equation [Eq. (3.4)], where pK_a^R is the pK_a of the substituted imidazole, pK_a^H is that of imidazole (R = H), σ_m is the meta electronic substituent constant, and ρ is the reaction constant (see Section II,E,2,a of Chapter 2). Imidazole has a pK_a of 6.80, and at physiological

$$pK_a^R = pK_a^H + \rho\sigma_m \tag{3.4}$$

temperature and pH, 20% of the molecules are in the protonated form. The imidazole in histamine under these conditions has a pK_a of 5.90. This indicates that the side chain is electron withdrawing, thus favoring tautomer **3.57a** (to the extent of 80%), and only 3% of the molecules are in the cationic form (**3.57b**). The pK_a of the imidazole in burimamide, however, is 7.25, indicating an electron-donating side chain which favors tautomer **3.57c**. The cation is one of the principal species, about 40% of the molecules. Therefore, even though the side chains in histamine and burimamide appear to be similar, they have opposite electronic effects on the imidazole ring.

On the assumption that the desired form of the imidazole should resemble that in histamine, the Smith, Kline & French group decided to convert the burimamide side chain to an electron-withdrawing group; however, they did not want to make a major structural modification. Incorporation of an electron-withdrawing atom into the side chain near the imidazole ring was contemplated, and the isosteric replacement of a methylene by a sulfur atom to give thiaburimamide (**3.59**, R = H) was carried out. A comparison of the physical properties of the two compounds (**3.56**, R = CH_3, and **3.59**, R = H) shows that they have similar van der Waals radii and bond angles, although the C—S bond is slightly longer than the C—C bond and is more flexible. A

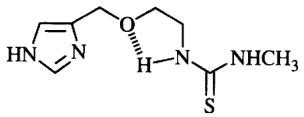


3.59

sulfur atom also is more hydrophilic than a methylene group; the log *P* for thiaburimamide is 0.16 and that for burimamide is 0.39. The pK_a of the imidazole in thiaburimamide was determined to be 6.25, indicating that the side chain was electron withdrawing and the favored tautomeric form was the same as in histamine (**3.57a**). Thiaburimamide is about three times more potent as a histamine H_2 receptor antagonist *in vitro* than burimamide.

A second way to increase the population of tautomer **3.57a** would be to introduce an electron-donating substituent at the 4-position of the ring, because electron-donating groups favor the form with the hydrogen on the adjacent nitrogen. Since 4-methylhistamine (**3.51**) is a known H_2 receptor agonist, there should be no steric problem with a 4-methyl group. However, the addition of an electron-donating group should increase the pK_a of the ring, thereby increasing the population of the cation (**3.57b**). Although the increase in tautomer **3.57a** is somewhat offset by the decrease in the total uncharged population, the overall effect was favorable. Metiamide (**3.59**, R = CH_3) has a pK_a identical with that of imidazole, indicating that the effect of the electron-withdrawing side chain exactly balanced the effect of the electron-donating 4-methyl group; the percentage of molecules in the charged form was 20%. The important result, however, is that metiamide is 8 to 9 times more potent than burimamide.

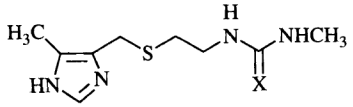
As an aside, it is interesting that the oxygen analog of burimamide also was synthesized in order to increase the electron-withdrawing effect of the side chain even further (oxygen is more electronegative than sulfur); however, oxaburimamide is less potent than burimamide. An explanation for this result is that intramolecular hydrogen bonding produces an unfavorable *conformationally restricted analog*, that is, a conformer stabilized by noncovalent phenomena (**3.60**).



3.60

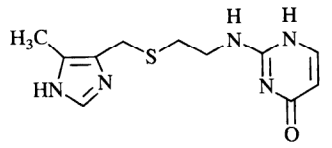
Metiamide was tested on 700 patients with duodenal ulcers, and it was found to produce significant increases in the healing rate with marked symptomatic relief. However, a few cases of granulocytopenia (deficiency of blood granulocytes and reduced bone marrow) developed. Even though this was a reversible side effect, it was undesirable, and it halted further clinical work with this compound.

The Smith, Kline & French group conjectured that the granulocytopenia that was associated with metiamide use was caused by the thiourea group; consequently, alternative substituents were sought. An isosteric replacement approach was taken. The corresponding urea (**3.61**, X = O) and guanidino (**3.61**, X = NH) analogs were synthesized and found to be 20 times less potent than metiamide. Of course, the guanidino analog would be positively charged at physiological pH, which could be the cause for the lower potency. Charton[61] found a Hammett relationship between the σ and pK_a values for N-substituted guanidines; consequently, if guanidino basicity were the problem, then substitution of the guanidino nitrogen with electron-withdrawing groups could lower the pK_a. In fact, cyanoguanidine and nitroguanidine have pK_a values of −0.4 and −0.9, respectively (compared with −1.2 for thiourea), a drop of about 14 pK_a units from that of guanidine. The corresponding cyanoguanidine (**3.61**, X = NCN; cimetidine) and nitroguanidine (**3.61**, X = NNO_2) were synthesized, and both were potent H_2 antagonists, comparable in potency to that of metiamide (cimetidine was slightly more potent than **3.61**, X = NNO_2).



3.61

Since strong electron-withdrawing substituents on the guanidino group favor the imino tautomer, the cyanoguanidino and nitroguanidino groups correspond to the thiourea structure (**3.61**, X = NCN, NNO_2, and S, respectively). These three groups are actually bioisosteres; they are all planar structures of similar geometries, are weakly amphoteric (weakly basic and acidic), being un-ionized in the pH range 4–11, are very polar, and are hydrophilic. The crystal structures of metiamide (**3.59**, R = CH_3) and cimetidine (**3.61**, X = NCN) are almost identical. The major difference in the two groups is that, whereas N,N′-disubstituted thioureas assume three stable conformers (Fig. 3.21; *Z*,*Z*, *Z*,*E*, and *E*,*Z*), N,N′-disubstituted cyanoguanidines appear to assume only two stable conformers (*Z*,*E* and *E*,*Z*). This suggests that the most stable conformer, the *Z*,*Z* conformer, is not the pharmacologically active form. An isocytosine analog (**3.62**) also was prepared (pK_a 4.0), which can



3.62

exist only in the *Z*,*Z* and *E*,*Z* conformations. It was about one-sixth as potent as cimetidine. However, the isocytosino group has a lower log *P* value (more

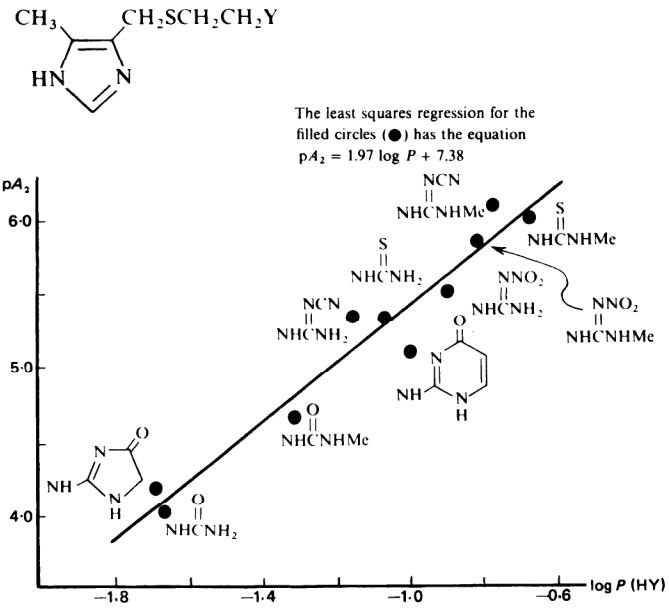
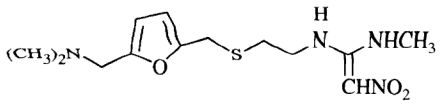


Figure 3.22. Linear free energy relationship between H_2 receptor antagonist activity and the partition coefficient. The least squares regression for the filled circles (●) has the equation $pA_2 = 1.97 \log P + 7.38$. [Reproduced with permission from Ganellin, C. R., and Parsons, M. E. (1982). *In* "Pharmacology of Histamine Receptors," p. 83. Wright-PSG, Bristol.]

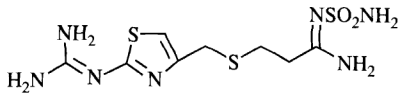
hydrophilic) than that of the *N*-methylcyanoguanidino group, and it was thought that lipophilicity may be an important physicochemical parameter. There was, indeed, a correlation found between the H_2 receptor antagonist activity *in vitro* and the octanol–water partition coefficient of the corresponding acid of the substituent Y (Fig. 3.22). Although increased potency correlates with increased lipophilicity, all of these compounds are fairly hydrophilic. Since the correlation was determined in an *in vitro* assay, membrane transport is not a concern; consequently, these results probably reflect a property involved with receptor interaction, not with transport. Therefore, it is not clear if the lower potency of the isocytosine analog is structure or hydrophilicity dependent.

Cimetidine was first marketed in the United Kingdom in 1976; therefore, it took only 12 years from initiation of the H_2 receptor antagonist program to commercialization. Subsequent to the introduction of cimetidine onto the U.S. drug market, two other H_2 receptor antagonists were approved, ranitidine (Glaxo Laboratories, **3.63**), which rapidly became the largest selling drug worldwide, and famotidine (Merck, Sharp & Dohme, **3.64**). It is obvious that an imidazole ring is not essential for H_2 receptor activity and that a positive

charge near the heterocyclic ring (the Me_2N— and guanidino groups of **3.63** and **3.64**, respectively, will be protonated at physiological pH) is not unfavorable.



3.63



3.64

The discovery of cimetidine is one of many examples of how the judicious use of physical organic chemistry can result in, at least, lead discovery, if not in drug discovery. Next, we turn our attention to a special class of receptors called enzymes, which are very important targets for drug design and drug action.

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