

# Chimica Farmaceutica

## Drug design

# Drug Design and Relationship of Functional Groups to Pharmacologic Activity

Medicinal chemistry is the discipline concerned with determining the influence of chemical structure on biological activity.

As such, it is necessary for the medicinal chemist to understand not only the mechanism by which a drug exerts its effect but also the physicochemical properties of the molecule. The term “physicochemical properties” refers to the influence of the organic functional groups within a molecule on its acid-base properties, water solubility, partition coefficient, crystal structure, stereochemistry, and so on. All these properties influence the absorption, distribution, metabolism excretion, and toxicity of the molecule. To design better medicinal agents, the medicinal chemist needs to understand the relative contributions that each functional group makes to the overall physicochemical properties of the molecule. Studies of this type involve modification of the molecule in a systematic fashion and determination of how these changes affect biological activity. Such studies are referred to as studies of structure-activity relationships (SAR) — That is, ***what structural features of the molecule contributes to, or takes away from, the desired biological activity of the molecule of interest.***

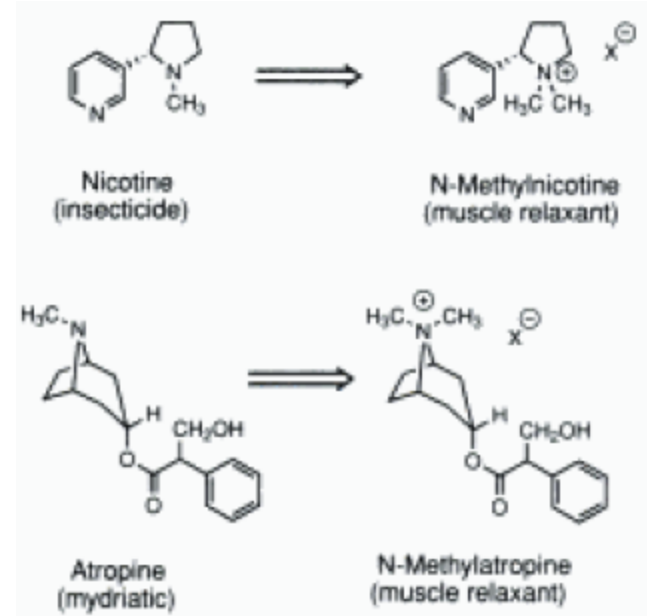
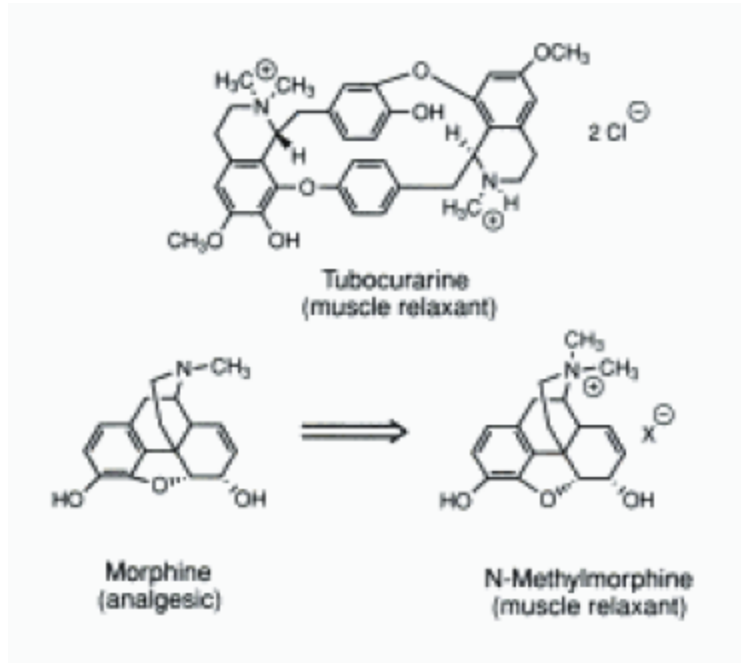
# Relationship Between Molecular Structure and Biological Activity

Early studies of the relationship between chemical structure and biological activity were conducted by Cramp Brown and Fraser in 1869. They showed that many compounds containing tertiary amine groups became muscle relaxants when converted to quaternary ammonium compounds. Compounds with widely differing pharmacologic properties, such as strychnine (a convulsant), morphine (an analgesic), nicotine (deterrent, insecticide), and atropine (anticholinergic), could be converted to muscle relaxants with properties similar to those of tubocurarine when methylated. Crum-Brown and Fraser therefore concluded that muscle-relaxant activity required a quaternary ammonium group within the chemical structure. This initial hypothesis was later disproven by the discovery of the natural neurotransmitter and activator of muscle contraction, acetylcholine. Even though Crum-Brown and Fraser's initial hypothesis concerning chemical structure and muscle relaxation was incorrect, it demonstrated the concept that molecular structure influences the biological activity of chemical compounds.

# Relationship Between Molecular Structure and Biological Activity

With the discovery by Crum-Brown and Fraser that quaternary ammonium groups could produce compounds with muscle-relaxant properties scientists began looking for other organic functional groups that would produce specific biological responses. The thinking during this time was that specific chemical groups or nuclei (rings), were responsible for specific biological effects. This led to the postulate, which took some time to disprove, that "one chemical group gives one biological action". Even after the discovery of acetylcholine by Loewi and Navrati, which effectively dispensed with Crum-Brown and Fraser's concept of all quaternary ammonium compounds being muscle relaxants, this was still considered to be dogma and took a long time to replace.

# Relationship Between Molecular Structure and Biological Activity



Acetylcholine, a neurotransmitter and muscle relaxant.

# Selectivity of Drug Action and Drug Receptors

Although the structures of many drugs or xenobiotics, or at least the composition of functional groups, were known at the start of the twentieth century, how these compounds exerted their effects was still a mystery. Utilizing his observations regarding the staining behavior of microorganisms, Ehrlich developed the concept of drug receptors. He postulated that certain "side chains" on the surfaces of cells were "complementary" to the dyes (or drug), thereby allowing the two substances to combine. In the case of antimicrobial compounds, this combining of the chemical to the "side chains" produced a toxic effect. This concept effectively was the first description of what later became known as the receptor hypothesis for explaining the biological action of chemical compounds. Ehrlich also discussed selectivity of drug action via the concept of a "magic bullet" for compounds that would eradicate disease states without producing undue harm to the organism being treated (i.e., the patient). This concept was later modified by Albert and generally is referred to as "selective toxicity." Utilizing this concept, Ehrlich developed organic arsenicals that were toxic to trypanosomes as a result of their irreversible reaction with mercapto groups (-SH) on vital proteins within the organism. The formation of As-S bonds resulted in death to the target organism. It was soon learned, however, that these compounds were toxic not only to the target organism but also to the host once certain blood levels of arsenic were achieved.

# Selectivity of Drug Action and Drug Receptors

The "paradox" that resulted after the discovery of acetylcholine — how one chemical group can produce two different biological effects (i.e., muscle relaxation and muscle contraction) — was explained by Ing using the actions of acetylcholine and tubocurarine as his examples, Ing hypothesized that both acetylcholine and tubocurarine act at the same receptor, but that one molecule fits to the receptor in a more complementary manner and "activates" it, causing muscle contraction, (Ing did not elaborate just how this activation occurred.) The blocking effect of the larger molecule, tubocurarine, could be explained by its occupation of part of the receptor, thereby preventing acetylcholine, the smaller molecule, from interacting with the receptor. With both molecules, the quaternary ammonium functional group is a common structural feature and interacts with the same region of the receptor. If one closely examines the structures of other compounds with opposing effects on the same pharmacologic system, this appears to be a common theme: ***Molecules that block the effects of natural neurotransmitters (antagonists) generally are larger in size than the native compound.*** Both agonists and antagonists share common structural features, however, thus providing support to the concept that the structure of a molecule, its composition and arrangement of chemical functional groups, determines the type of pharmacologic effect that it possesses (i.e., SAR). Thus, compounds that are muscle relaxants acting via the cholinergic nervous system will possess a quaternary ammonium or protonated tertiary ammonium group and will be larger than acetylcholine.

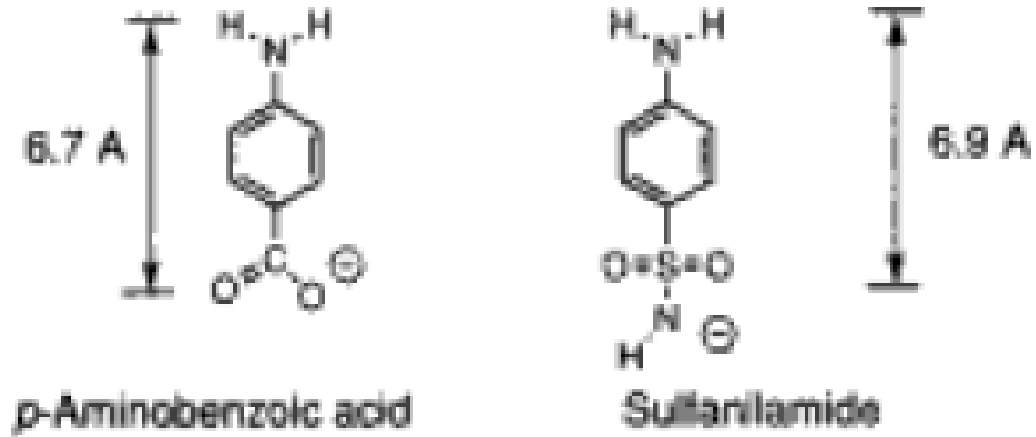
# Selectivity of Drug Action and Drug Receptors

Structure-activity relationships are the underlying principle of medicinal chemistry. **Similar molecules exert similar biological actions in a qualitative sense.** A corollary to this is that structural elements (functional groups) within a molecule most often contribute in an additive manner to the physicochemical properties of a molecule and, therefore, to its biological action. One need only peruse the structures of drug molecules in a particular pharmacologic class to become convinced of this (e.g., histamine H1 antagonists, histamine H2 antagonists, and  $\beta$ -adrenergic antagonists). The objective of medicinal chemists in their quest for better medicinal agents (drugs) is to discover what functional groups within a specific structure are important for its pharmacologic activity and how can these groups be modified to produce more potent, selective, and safer compounds.

An example of how different functional groups can yield compounds with similar physicochemical properties is shown with sulfanilamide antibiotics. The structures of sulfanilamide and p-aminobenzoic acid (PABA) are shown. In 1910, Woods demonstrated that PABA was capable of reversing the antibacterial action of sulfanilamide (and other sulfonamides antibacterials) and that both PABA and sulfanilamide had similar steric and electronic properties. Both compounds contain acidic functional groups, with PABA containing an aromatic carboxylic acid and sulfanilamide an aromatic sulfonamide. When ionized at physiological pH, both compounds have a similar electronic configuration, and the distance between the ionized acid and the weakly basic amino group also is very similar. It should therefore be no surprise that sulfanilamide acts as an antagonist to PABA metabolism in bacteria.



# Selectivity of Drug Action and Drug Receptors



# PHYSICOCHEMICAL PROPERTIES OF DRUGS:

## Acid-Base Properties

The human body is 70 to 75% water, which amounts to approximately 51 to 55 L of water for a 73 kg individual. For an average drug molecule with a molecular weight of 200 g/mol and a dose of 20 mg, this leads to a solution concentration of approximately  $2 \times 10^{-6}$  M. When considering the solution behavior of a drug within the body, we therefore are dealing with a dilute solution, for which the Bronsted-Lowry acid-base theory is most appropriate for explaining and predicting acid-base behavior. This is a very important concept in medicinal chemistry because the acid-base properties of drug molecules directly affect absorption, excretion, and compatibility with other drugs in solution.

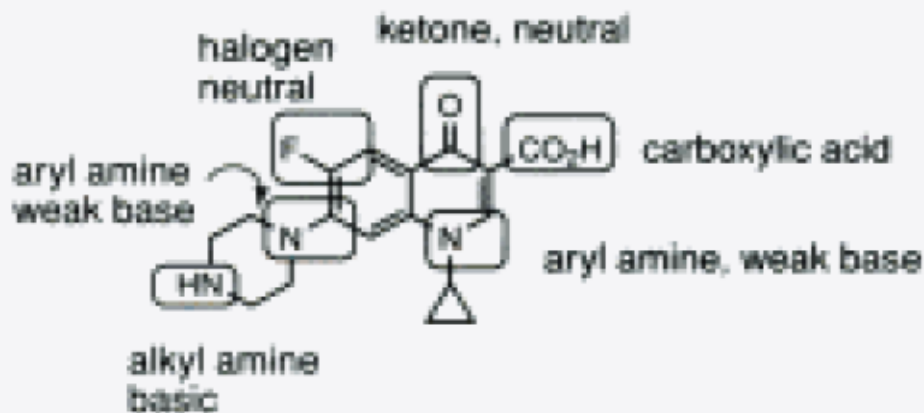
From general principles, it is possible to predict if a molecule is going to be ionized or unionized at a given pH simply by knowing if the functional groups on the molecule are acidic or basic. To be able to quantitatively predict the degree of ionization of a molecule, however, one must know the pKa values of the acidic and basic functional groups that are present and the pH of the environment to which the compound will be exposed. The Henderson-Hasselbalch equation can be used to calculate the percentage ionization of a compound at a given pH (this equation was used to calculate the major forms of ciprofloxacin).

$$pK_a = pH + \log \frac{[\text{acid form}]}{[\text{base form}]}$$

# PHYSICOCHEMICAL PROPERTIES OF DRUGS: Acid-Base Properties

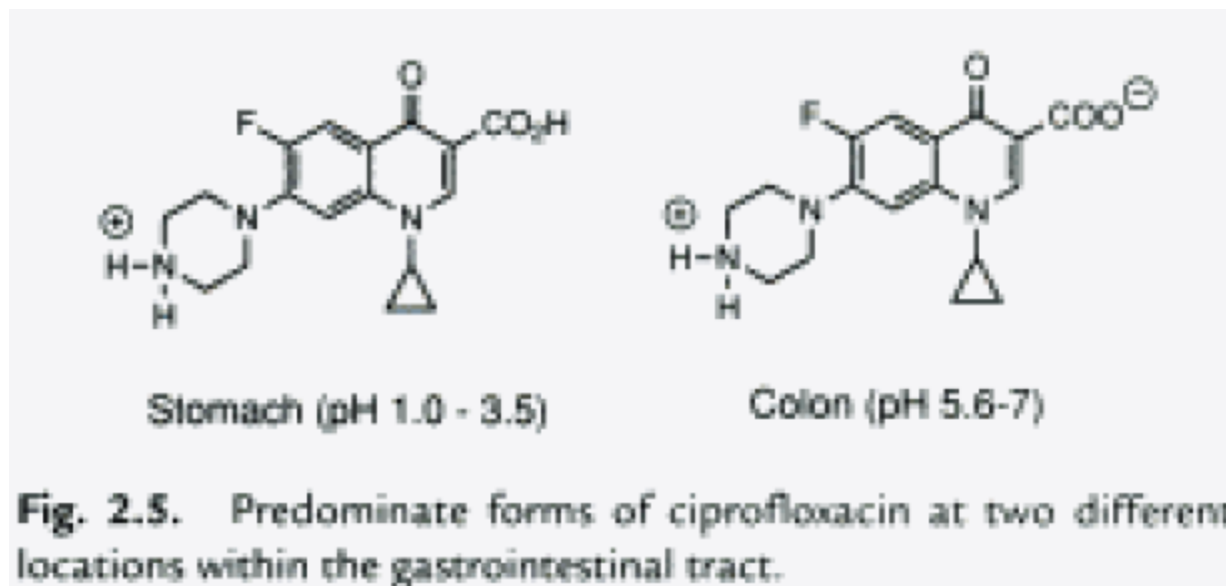
The key to understanding the use of the Henderson-Hasselbalch equation for calculating percentage ionization is to realize that this equation relates a constant,  $pK_a$ , to the ratio of acidic form to the basic form of the drug. Because  $pK_a$  is a constant for any given molecule, the ratio of acid to base will determine the pH of the solution. Conversely, a given pH determines the ratio of acid to base.

When dealing with a base, the student must recognize that the conjugate acid is the ionized form of the drug. Thus, as one should expect, a base behaves in a manner opposite to that of an acid. It is very important to recognize that for a base, the  $pK_a$  refers to the conjugate acid or ionized form of the compound.



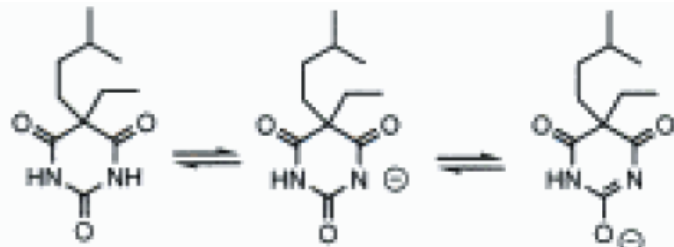
**Fig. 2.4.** Chemical structure of ciprofloxacin showing the various organic functional groups.

# PHYSICOCHEMICAL PROPERTIES OF DRUGS: Acid-Base Properties



# PHYSICOCHEMICAL PROPERTIES OF DRUGS:

## Acid-Base Properties: Predicting the Degree of Ionization of a Molecule



Acid form  
pK<sub>a</sub> 8.0

Conjugate base

Question: At a pH of 7.4, what is the percent ionization of amobarbital?

Answer:  $8.0 = 7.4 + \log \frac{[\text{acid}]}{[\text{base}]}$

$$0.6 = \log \frac{[\text{acid}]}{[\text{base}]}$$

$$10^{0.6} = \frac{[\text{acid}]}{[\text{base}]} = \frac{3.98}{1}$$

$$\% \text{ acid form} = \frac{3.98 \times 100}{4.98} = 79.9\%$$

**Fig. 2.6.** Calculation of percentage ionization of amobarbital. Calculation indicates that 80% of the molecules are in the acid (or protonated) form, leaving 20% in the conjugate base (ionized) form.



Base form

Conjugate acid form  
pK<sub>a</sub> 9.4

Question: What is the % ionization of phenylpropanolamine at pH 7.4?

Answer:  $9.4 = 7.4 + \log \frac{[\text{acid}]}{[\text{base}]}$

$$2.0 = \log \frac{[\text{acid}]}{[\text{base}]}$$

$$10^2 = \frac{[\text{acid}]}{[\text{base}]} = \frac{100}{1}$$

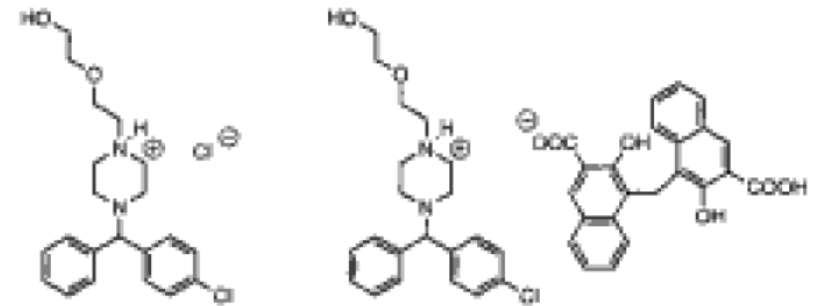
$$\% \text{ ionization} = \frac{100 \times 100}{101} = 99\%$$

**Fig. 2.7.** Calculation of percentage ionization of phenylpropanolamine. Calculation indicates that 99% of the molecules are in the acid form, which is the same as the percentage ionization.

# PHYSICOCHEMICAL PROPERTIES OF DRUGS:

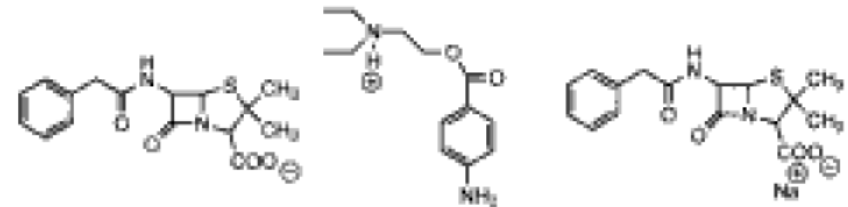
## Water Solubility of Drugs

The solubility of a drug molecule in water greatly affects the routes of administration that are available as well as its absorption, distribution, and elimination. Two key concepts to keep in mind when considering the water (or fat) solubility of a molecule are the **hydrogen bond-forming** potential of the functional groups in the molecule and the **ionization** of functional groups.



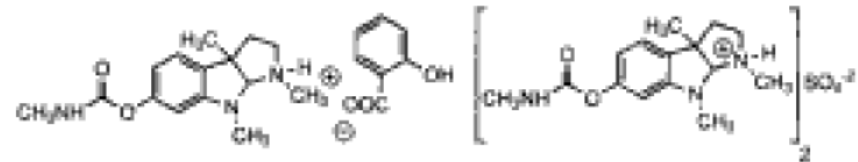
Hydroxyzine hydrochloride  
(1g/mL)

Hydroxyzine pamoate  
(1g/1000 mL)



Penicillin G procaine  
(1g/250 mL)

Penicillin G sodium  
(1g/40 mL)



Physostigmine salicylate  
(1g/75 mL)

Physostigmine sulfate  
(1g/4 mL)

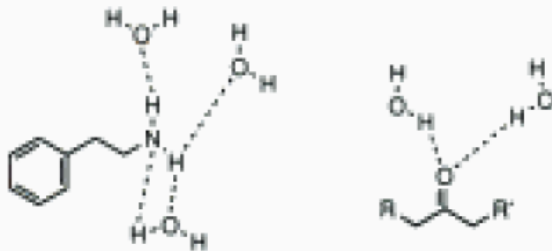


Fig. 2.8. Examples of hydrogen-bonding between water and hypothetical drug molecules.

Fig. 2.10. Water solubilities of different salt forms of selective drugs.

# PHYSICOCHEMICAL PROPERTIES OF DRUGS:

## Predicting Water Solubility: Empiric Approach

Lemke has developed an empiric approach to predicting the water solubility of molecules based on the carbon-solubilizing potential of several organic functional groups. If the solubilizing potential of the functional groups exceeds the total number of carbon atoms present, then the molecule is considered to be water soluble. Otherwise, it is considered to be water insoluble. Functional groups that can interact either through intramolecular hydrogen or ion-ion interactions will decrease the solubilizing potential of each group. It is difficult to quantitate how much such interactions will take away from water solubility, but recognizing these interactions will allow one to explain anomalous results.

Table 2.5. Water-solubilizing Potential of Organic Functional Groups in a Mono- or Polyfunctional Molecule

Functional Group	Monofunction Molecule	Polyfunctional Molecule
Alcohol	5 to 6 carbons	3 to 4 carbons
Phenol	6 to 7 carbons	3 to 4 carbons
Ether	4 to 5 carbons	2 carbons
Aldehyde	4 to 5 carbons	2 carbons
Ketone	5 to 6 carbons	2 carbons
Amine	6 to 7 carbons	3 carbons
Carboxylic acid	5 to 6 carbons	3 carbons
Ester	6 carbons	3 carbons
Amide	6 carbons	2 to 3 carbons
Urea, carbonate, carbamate		2 carbons

Water solubility is defined as greater than 1% solubility (9).

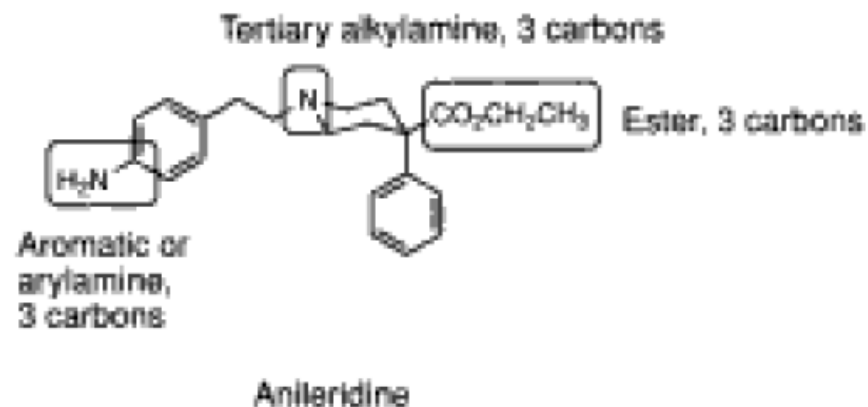


Fig. 2.13. Identification of functional groups in anileridine.

# PHYSICOCHEMICAL PROPERTIES OF DRUGS:

## Predicting Water Solubility: Analytical Approach

Another method for predicting water solubility involves calculating an approximate logP or log of the partition coefficient for a molecule. This approach is based on an approximation method developed by Cates and discussed in Lemke. In this approach, one sums the hydrophobic or hydrophilic properties of each functional group present in the molecule. Before we can calculate logP values, we must first digress to a brief explanation of the concept of partition coefficient.

In its simplest form, the partition coefficient, P, refers to the ratio of the concentrations of drug in octanol to that in water. Octanol is used to mimic the amphiphilic nature of lipid. because it has a polar head group (primary alcohol) and a long hydrocarbon chain, or tail, such as that of fatty acids, which make up part of a lipid membrane. Because P is logarithmically related to free energy, it generally is expressed as logP and therefore, is the sum of the hydrophobic and hydrophilic characteristics of the organic functional groups making up the structure of the molecule. Thus, logP is a measure of the solubility characteristics of the entire molecule. Because each organic functional group contained within the molecule contributes to the overall hydrophobic/hydrophilic nature of the molecule, a hydrophobic/hydrophilic value (the hydrophobic substituent constant.  $\pi$ ) can be assigned to each organic functional group.

$$\text{LogP} = \sum \pi \text{ (fragments)}$$



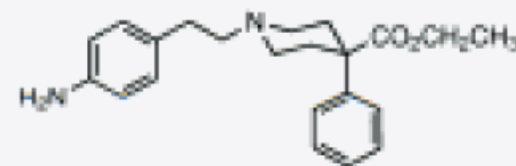
# PHYSICOCHEMICAL PROPERTIES OF DRUGS:

## Predicting Water Solubility: Analytical Approach

When calculating logP from hydrophobic substituent constants, the sum is usually referred to as  $\log P_{\text{calc}}$  or ClogP to distinguish it from an experimentally determined value ( $\log P$  or MlogP). Over the years, extensive tables of  $\pi$  values have been compiled for organic functional groups and molecular fragments.

Table 2.6. Hydrophilic-lipophilic Values ( $\pi$  V) for Organic Fragments (10)

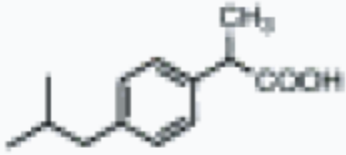
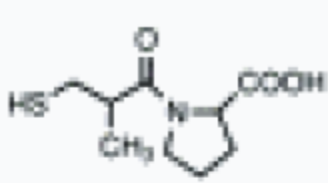
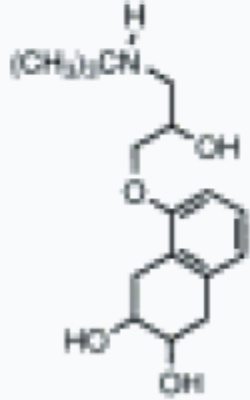
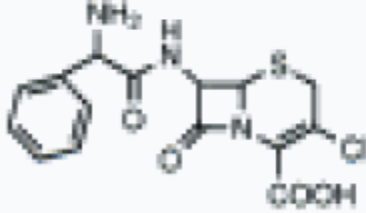
Fragments	$\pi$ Value
C (aliphatic)	+0.5
Phenyl	+2.0
Cl	+0.5
O <sub>2</sub> NO (nitrate ester)	+0.2
IMHB (intramolecular hydrogen bond)	+0.65
S	0.0
O=C-O (carboxyl)	-0.7
O=C-N (amide, imide)	-0.7
O (hydroxyl, phenol, ether)	-1.0
N (amine)	-1.0
O <sub>2</sub> N (aliphatic)	-0.85
O <sub>2</sub> N (aromatic)	-0.28



Fragments	$\pi$
2 amines	-2.0
9 aliphatic carbons	+3.5
2 phenyl rings	+4.0
1 ester	-0.7
logP	+4.8

Fig. 2.14. Calculation of logP for anileridine.

# PHYSICOCHEMICAL PROPERTIES OF DRUGS: Predicting Water Solubility: Analytical Approach

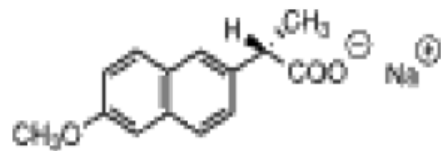
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# STEREOCHEMISTRY AND DRUG ACTION

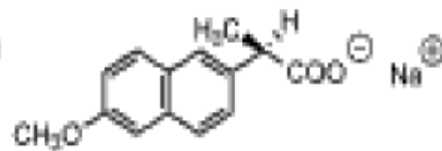
Stereoisomers are compounds containing the same number and kinds of atoms, the same arrangement of bonds, but different three-dimensional structures: in other words, they only differ in the three-dimensional arrangements of atoms in space. Stereoisomers are subdivided into two types, enantiomers and diastereoisomers. Enantiomers are compounds for which the three-dimensional arrangement of atoms is such that they are nonsuperimposable mirror images. Diastereoisomers are all stereoisomer compounds that are not enantiomers. Thus, the term "diastereoisomer" includes compounds containing double bonds (geometric isomers) as well as ring systems. Unlike enantiomers diastereoisomers exhibit different physicochemical properties, including, but not limited to, melting point, boiling point, solubility, and chromatographic behavior. These differences in physicochemical properties allow the separation of diastereoisomers from mixtures utilizing standard chemical separation techniques, such as column chromatography or crystallization. Enantiomers cannot be separated using such techniques unless a chiral environment is provided or they are converted to diastereoisomers.

# STEREOCHEMISTRY AND DRUG ACTION

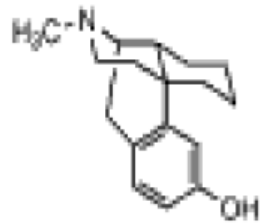
## ENANTIOMERS



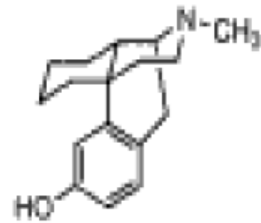
(S)-(+)-naproxen sodium



(R)-(-)-naproxen sodium

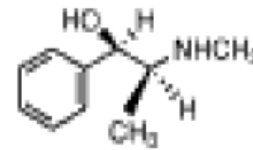


Levorphanol (anagesic)

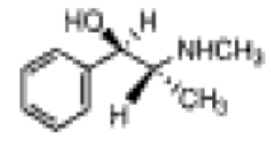


Dextrophan (antitussive)

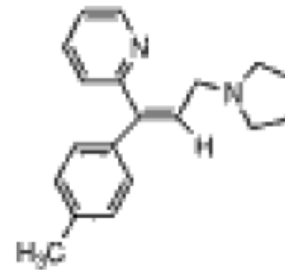
## DIASTEREOISOMERS



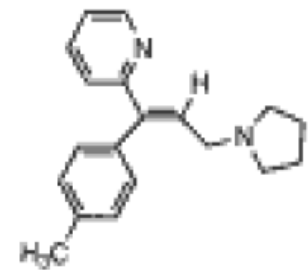
(-)-Ephedrine (1R,2S)



(-)-Pseudoephedrine (1R,2R)



(Z)-triprolidine (inactive)



(E)-triprolidine (active)

# STEREOCHEMISTRY AND DRUG ACTION

The physicochemical properties of a drug molecule are dependent not only on what functional groups are present in the molecule but also on the spatial arrangement of these groups. This becomes an especially important factor when a molecule is subjected to an asymmetric environment, such as the human body. Because proteins and other biological macromolecules are asymmetric in nature, how a particular drug molecule interacts with these macromolecules is determined by the three-dimensional orientation of the organic functional groups that are present. If crucial functional groups are not occupying the proper spatial region surrounding the molecule, then productive bonding interactions with the biological macromolecule (or receptor) will not be possible, potentially negating the desired pharmacological effect. If however, these functional groups are in the proper three-dimensional orientation, the drug can produce a very strong interaction with its receptor. It therefore is very important for the medicinal chemist developing a new molecular entity for therapeutic use to understand not only what functional groups are responsible for the drug's activity but also what three-dimensional orientation of these groups is needed.

# STEREOCHEMISTRY AND DRUG ACTION

Approximately one in every four drugs currently on the market can be considered to be an isomeric mixture, yet for many of these compounds, the biological activity may reside in only one isomer (or at least predominate in one isomer). The majority of these isomeric mixtures are what are referred to as "racemic mixtures" (or "racemates"). These are compounds, usually synthetic, that contain equal amounts of both possible enantiomers, or optical isomers. Enantiomers also are referred to as chiral compounds, antipodes, or enantiomorphs. When introduced into an asymmetric, or chiral, environment, such as the human body, enantiomers will display different physicochemical properties, producing significant differences in their pharmacokinetic and pharmacodynamic behavior. Such differences can result in adverse side effects or toxicity, because one or more of the isomers may exhibit significant differences in absorption (especially active transport), serum protein binding, and metabolism. With the latter, one isomer may be converted into a toxic substance or may influence the metabolism of another drug.

The basic concepts of stereochemistry will be not reviewed as previously studied in the organic chemistry course.

# STEREOCHEMISTRY AND DRUG ACTION

## Stereochemistry and Biological Activity: Easson-Stedman Hypothesis

In 1886, Piutti reported different physiologic actions for the enantiomers of asparagine, with (+)-asparagine having a sweet taste and (-)-asparagine a bland one. This was one of the earliest observations that enantiomers can exhibit differences in biological action. In 1933, Easson and Stedman reasoned that differences in biological activity between enantiomers resulted from selective reactivity of one enantiomer with its receptor. They postulated that such interactions require a minimum of a three-point fit to the receptor.

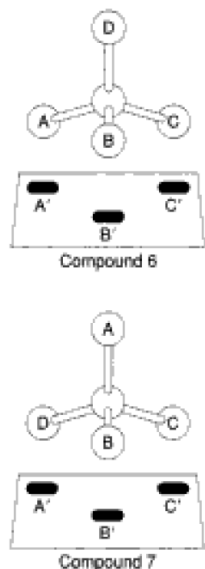


Fig. 2.18. Optical isomers. Only in compound 6 do the functional groups A, B, and C align with the corresponding sites of binding on the asymmetric surface.

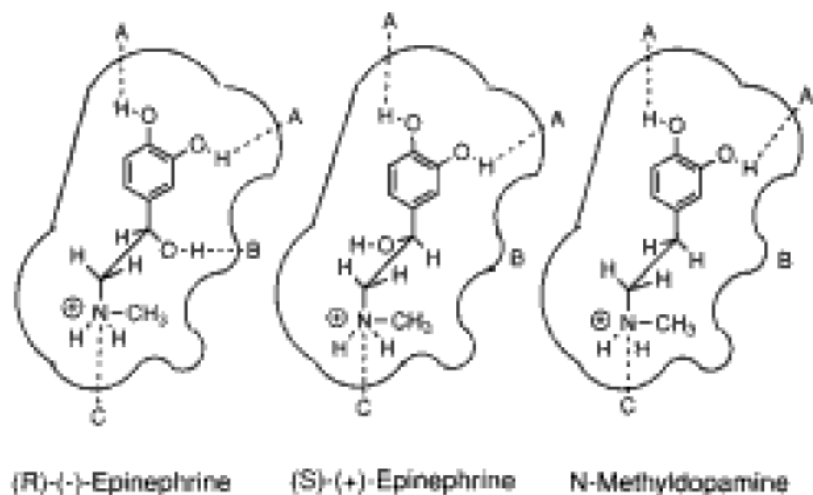


Fig. 2.19. Drug receptor interaction of (R)-(-)-epinephrine, (S)-(+)-epinephrine, and N-methyldopamine.

# STEREOCHEMISTRY AND DRUG ACTION

## Stereochemistry and Biological Activity: Easson-Stedman Hypothesis

The Easson-Stedman Hypothesis states that the more potent enantiomer must be involved in a minimum of three intermolecular interactions with the receptor surface and that the less potent enantiomer only interacts with two sites. This can be illustrated by looking at the differences in vasopressor activity of (R)-(-)-Epinephrine, (S)-(+)-epinephrine and the achiral N-methyldopamine. With (R)-(-)-Epinephrine, the three points of interaction with the receptor site are the substituted aromatic ring, B-hydroxyl group, and the protonated secondary ammonium group. All three functional groups interact with their complementary binding sites on the receptor surface, producing the necessary interactions that stimulate the receptor. With (S)-(+)-Epinephrine, only two interactions are possible (the protonated secondary ammonium and the substituted aromatic ring). The B-hydroxyl group occupies the wrong region of space and therefore, cannot interact properly with the receptor. N-methyldopamine can achieve the same interactions with the receptor as (S)-(+)-Epinephrine: therefore it is not surprising that its vasopressor response is the same as that of (S)-(+)-Epinephrine and less than that of (R)-(-)-Epinephrine.



# STEREOCHEMISTRY AND DRUG ACTION

## Stereochemistry and Biological Activity

Not all stereoselectivity seen with enantiomers can be attributed to differences in reactivity at the receptor site. Differences in biological activity also can result from differences in the ability of each enantiomer to reach the receptor site. Because the biological system encountered by the drug is asymmetric, each enantiomer may experience selective penetration of membranes, metabolism, and absorption at sites of loss (e.g., adipose tissue) or excretion. Not all of these processes may be encountered by a particular enantiomer, but such processes may provide enough of an influence to cause one enantiomer to produce a significantly better pharmacologic effect than the other. Conversely, such processes also may contribute to untoward effects of a particular enantiomer.

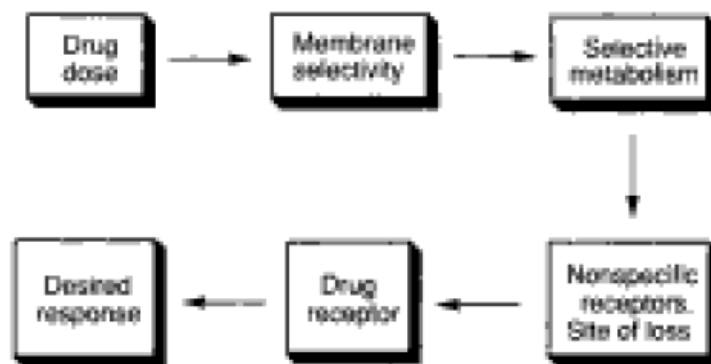
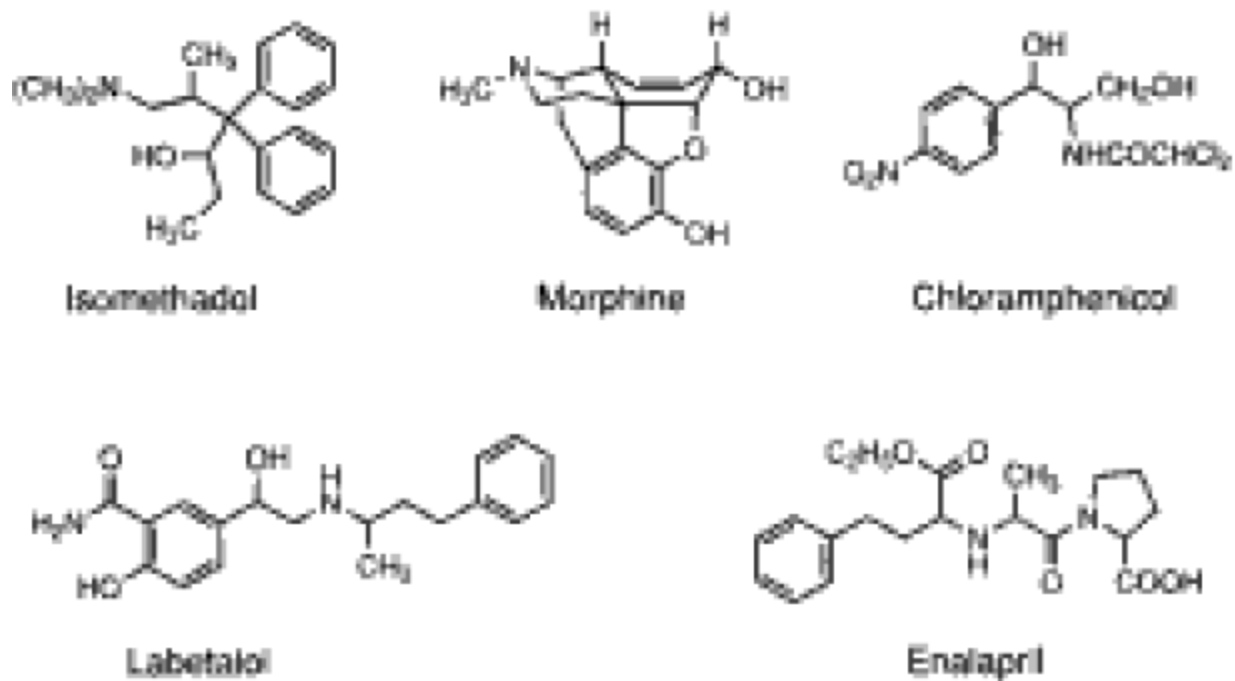


Fig. 2.20. Selective phases to which optical isomers may be subjected before biological response.

# STEREOCHEMISTRY AND DRUG ACTION

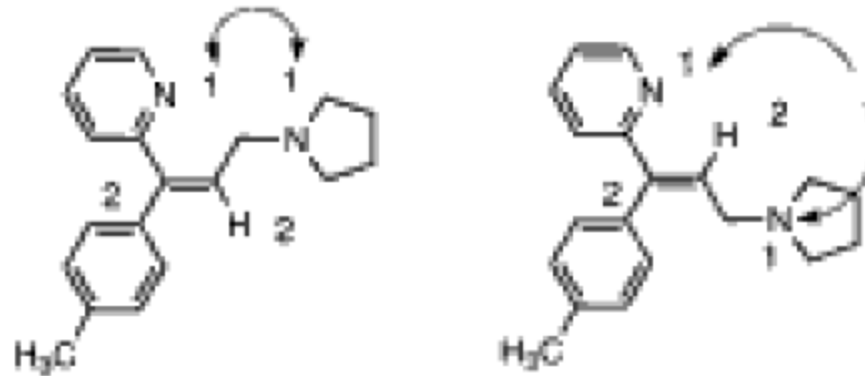
## Stereochemistry and Biological Activity



**Fig. 2.22.** Examples of chiral drugs with two or more asymmetric centers.

# STEREOCHEMISTRY AND DRUG ACTION

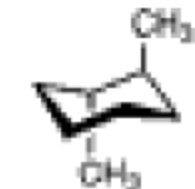
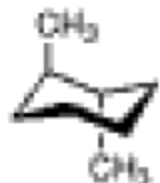
## Stereochemistry and Biological Activity



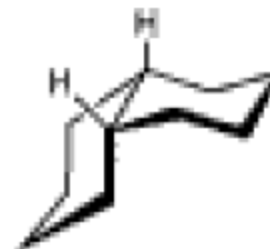
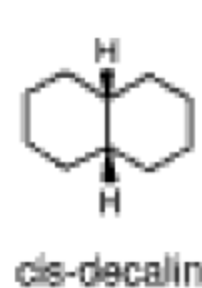
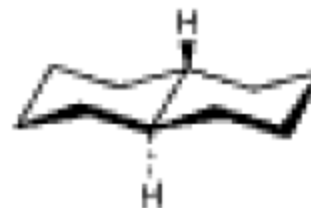
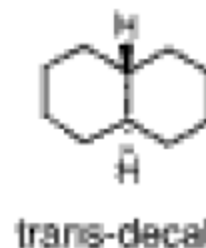
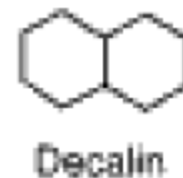
1. Geometric isomers of triprolidine.

# STEREOCHEMISTRY AND DRUG ACTION

## Stereochemistry and Biological Activity

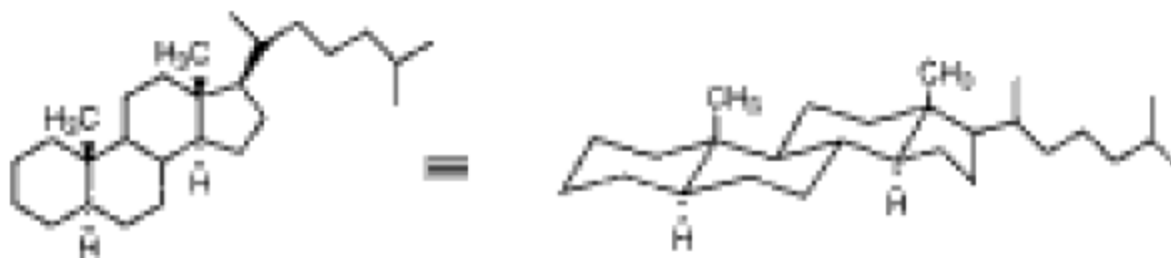


Diastereomers of 1,2-dimethylcyclohexane.

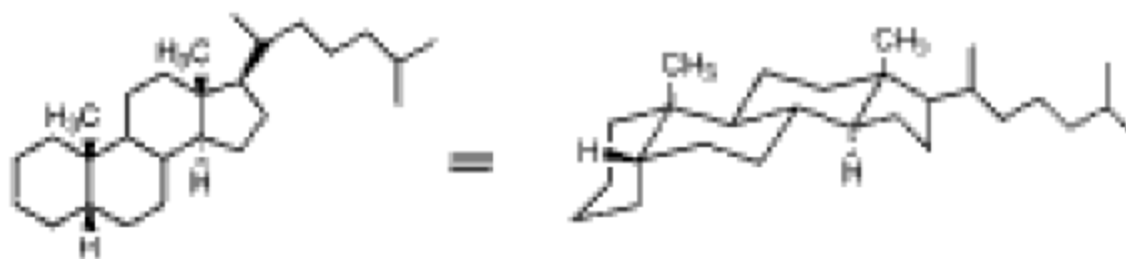


# STEREOCHEMISTRY AND DRUG ACTION

## Stereochemistry and Biological Activity



5 $\alpha$ -Cholestane

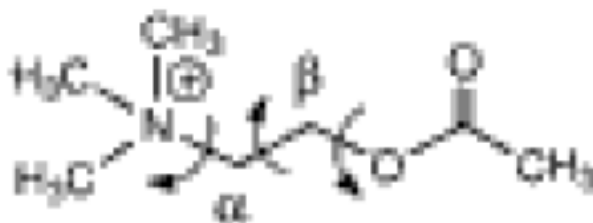


5 $\beta$ -Cholestane

# STEREOCHEMISTRY AND DRUG ACTION

## Conformational Isomerism and Biological Activity

With conformational isomerism, we are dealing with a dynamic process — that is, isomerization takes place via rotation about one or more single bonds. Such bond rotation results in nonidentical spatial arrangement of atoms in a molecule. Changes in spatial orientation of atoms because of bond rotation results in different conformations (or rotamers), whereas conversion of one enantiomer into another (or diastereoisomer) requires the breaking of bonds, which has a much higher energy requirement than rotation around a single bond. The neurotransmitter acetylcholine can be used to demonstrate the concept of conformational isomers.



Acetylcholine

# STEREOCHEMISTRY AND DRUG ACTION

## Conformational Isomerism and Biological Activity

Each single bond within the acetylcholine molecule is capable of undergoing rotation, and at room temperature, such rotations readily occur. Even though rotation around single bonds was shown by Kemp and Pitzer in 1936 not to be free but, rather, to have an energy barrier, this barrier is sufficiently low that at room temperature, acetylcholine exists in many interconvertible conformations. Close observation reveals that rotation around the central  $C\alpha$ - $C\beta$  bond produces the greatest spatial rearrangement of atoms compared to rotation around any other bond within the molecule. In fact, several rotatable bonds in acetylcholine produce redundant structures, because all of the atoms attached to one end of some bonds are identical, resulting in no change in spatial arrangement of atoms (methyls). When viewed along the  $C\alpha$ - $C\beta$  bond, acetylcholine can be depicted in the Newman projections. When the ester and trimethylammonium group are  $180^\circ$  apart, the molecule is said to be in the anti or staggered, conformation (or conformer or rotamer). This conformation allows maximum separation of the functional groups and, therefore, considered to be the most stable conformation energetically. Other conformations possibly are more stable if factors other than steric interactions come into play (e.g., intramolecular hydrogen bonds).

# STEREOCHEMISTRY AND DRUG ACTION

## Conformational Isomerism and Biological Activity

Rotation of one end of the  $C_{\alpha}$ - $C_{\beta}$  bond by  $120^{\circ}$  or  $240^{\circ}$  results in the two gauche, or skew, conformations. These are considered to be less stable than the anticonformer, although some studies suggest that an electrostatic attraction between the electron-poor trimethylammonium and electron-rich ester oxygen stabilizes this conformation. Rotation by  $60^{\circ}$ ,  $180^{\circ}$ , and  $240^{\circ}$  produce conformations in which all of the atoms overlap, or what are referred to as eclipsed conformations. These are the least stable conformers. An interesting observation can be made with the two gauche conformers. These conformers are not distinct molecules, and they only exist for a transient period of time at room temperature. If these could be "frozen" into the conformations shown, however, they would be nonsuperimposable mirror images or enantiomers. Thus, a compound that is achiral, such as acetylcholine, can exhibit prochirality if certain conformational isomers can be formed. It is quite possible that such a situation could exist when acetylcholine binds to one of its receptors.

Studies have suggested that the gauche conformation is the form that binds to the nicotinic receptor, whereas the anti form, which is achiral, binds to the muscarinic receptor.



# STEREOCHEMISTRY AND DRUG ACTION

## Conformational Isomerism and Biological Activity

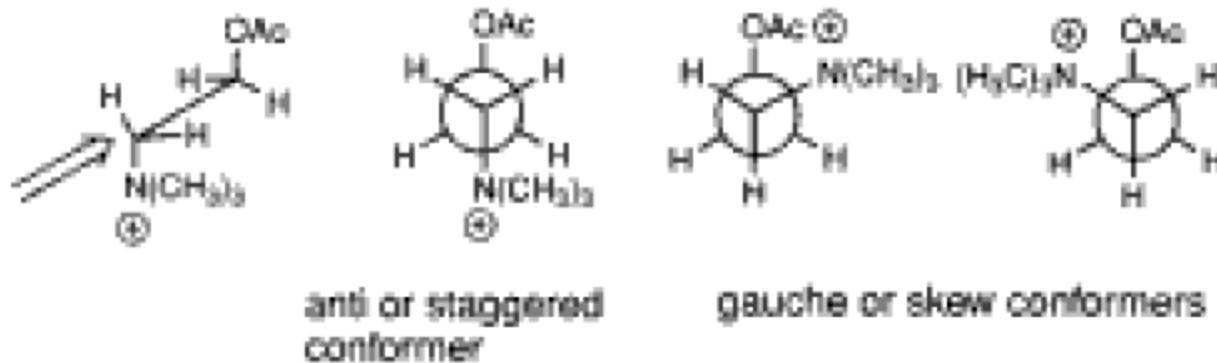


Fig. 2.26. Anti and gauche conformations of acetylcholine.

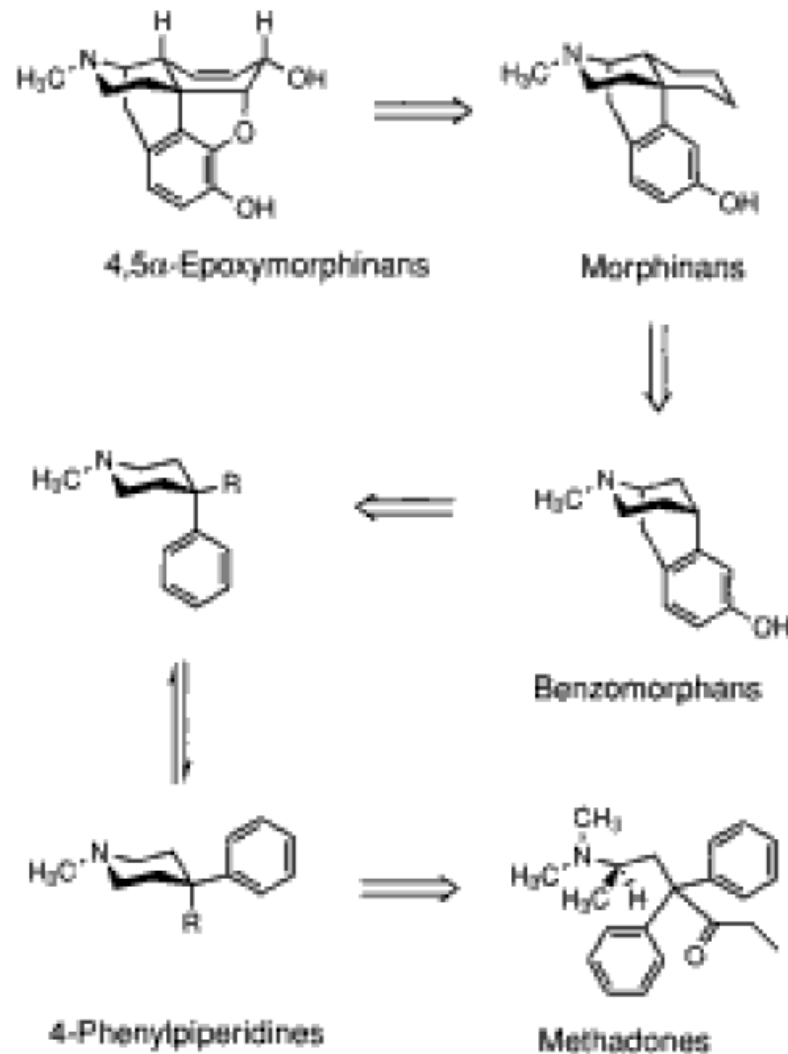
# REFINEMENT OF THE LEAD STRUCTURE

## Determination of the Pharmacophore

Once a lead compound has been discovered for a particular therapeutic use, the next step is to determine the pharmacophore for this compound. The pharmacophore of a drug molecule is that portion of the molecule containing the essential organic functional groups that directly interact with the receptor active site and therefore, confers on the molecule the biological activity of interest. Because drug-receptor interactions can be very specific, the pharmacophore may constitute a small portion of the molecule. It has been found on several occasions that what seem to be very complex molecules can be reduced to simpler structures with retention of the desired biological action. An example of this is the narcotic analgesic morphine, which is a tetracyclic compound with five chiral centers. Not only would simplification of the structure possibly provide molecules with fewer side effects, a reduction in the number of chiral centers would greatly simplify the synthesis of morphine derivatives and, thereby, decrease cost. It can be readily seen from the figure that the pharmacophore of morphine must consist of a tertiary alkylamine that is at least four atoms away from an aromatic ring.

# REFINEMENT OF THE LEAD STRUCTURE

## Determination of the Pharmacophore



Chimica Farmaceutica **Fig. 2.30.** Morphine pharmacophore and its relationship to analgesic derivatives.

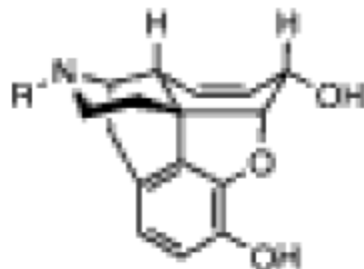
# REFINEMENT OF THE LEAD STRUCTURE

## Alterations in Alkyl Chains: Chain Length, Branching, and Rings

Alterations in alkyl chains, such as increasing or decreasing chain length (homologation), branching, and changing ring size, can have profound effects on the potency and pharmacologic activity of the molecule. Simply changing the length of an alkyl chain by one  $\text{CH}_2$  unit or branching the chain will alter the lipophilic character of the molecule and, therefore, its properties of absorption, distribution, and excretion. If the alkyl chain is directly involved in the receptor interaction, then chain length and branching can alter the binding characteristics. Molecules that are conformationally flexible may become less flexible if branching is introduced at a key position of an alkyl chain. Changes in conformation will affect the spatial relationship of functional groups in the molecule, thereby influencing receptor binding. Changes as small as one  $\text{CH}_2$  unit may seem trivial at first, but in many instances, such small changes are important aspects in the design of analogues.

# REFINEMENT OF THE LEAD STRUCTURE

## Alterations in Alkyl Chains: Chain Length, Branching, and Rings




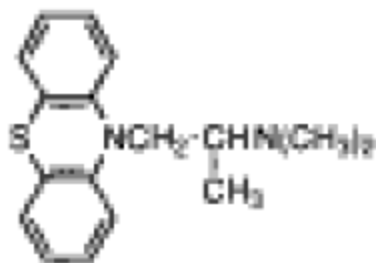
R	Pharmacological activity
-CH <sub>3</sub>	Analgesic (morphine)
-CH <sub>2</sub> CH <sub>3</sub>	Opioid agonist activity decreased
-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Opioid antagonist activity increased
-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Inactive as opioid agonist or antagonist
-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Opioid antagonist activity increased
-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	
-CH <sub>2</sub> CH <sub>2</sub> - 	14X potency of morphine

Fig. 2.31. Effect of alkyl chain length on activity of morphine.

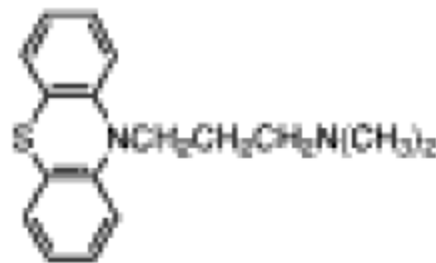
# REFINEMENT OF THE LEAD STRUCTURE

## Alterations in Alkyl Chains: Chain Length, Branching, and Rings

Branching of alkyl chains also can produce drastic changes in potency and pharmacologic activity. If the mechanism of action is closely related to the lipophilicity of the molecule, then branching of a hydrocarbon chain will result in a less lipophilic compound and significantly altered biological effect. This decrease in lipophilicity as the result of hydrocarbon chain branching results from the chain becoming more compact and therefore, produces less disruption of the hydrogen bonding network of water. If the hydrocarbon chain is directly involved in receptor interactions, then branching can produce major changes in pharmacologic activity.



Promethazine



Promazine

# REFINEMENT OF THE LEAD STRUCTURE

## Alterations in Alkyl Chains: Chain Length, Branching, and Rings

Position isomers of substituents on aromatic rings also may possess different pharmacologic properties. Substituents on aromatic rings can alter the electron distribution throughout the ring, which in turn can affect how the ring interacts with the receptor. Ring substituents also may influence the conformation of a flexible molecule, especially if they are located ortho to flexible side chains and can participate in steric or electronic intramolecular interactions. Ring substituents influence the conformations of adjacent substituents via steric interactions and may significantly affect receptor interactions. Aromatic methoxy groups ortho to two other substituents take on a conformation perpendicular to the plane of the aromatic ring in hallucinogenic phenylalkylamines and can explain the lack of hallucinogenic activity in these compounds.

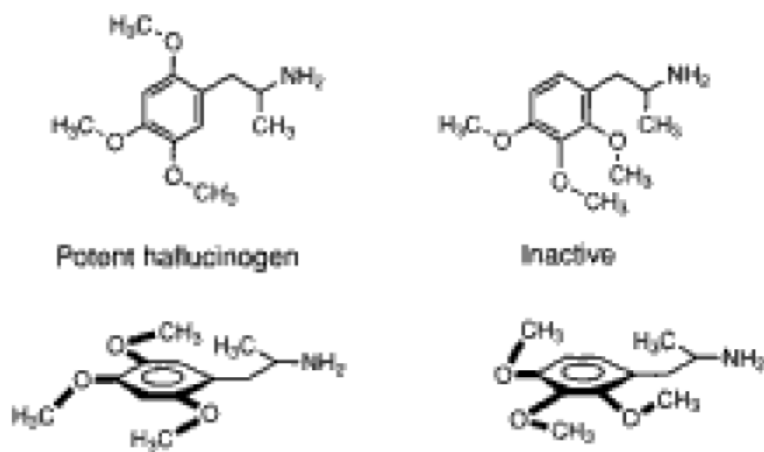


Fig. 2.32. Effect of positional isomers on structural conformation and biological activity.

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

When a lead compound is first discovered for a particular disease state, it often lacks the required potency and pharmacokinetic properties suitable for making it a viable clinical candidate. These may include undesirable side effects, physicochemical properties, other factors that affect oral bioavailability and adverse metabolic or excretion properties. These undesirable properties could be the result of specific functional groups in the molecule. The medicinal chemist therefore must modify the compound to reduce or eliminate these undesirable features without losing the desired biological activity. Replacement or modification of functional groups with other groups having similar properties is known as "**isosteric replacement**" or "**bioisosteric replacement**"



# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

## The molecular number

**Allen**, in 1918 defined the *molecular number* of a compound in a similar way of the atomic number:

$$N = aN_1 + bN_2 + cN_3 + \dots + zN_i$$

where  $N$  = molecular number

$N_1, N_2, N_3, \dots, N_i$  = respective atomic numbers of each element of the molecule.

$a, b, \dots, z$  = number of atoms of each element present in the molecule.

*Example:* Comparison of the ammonium and the sodium cations. The atomic number of nitrogen is 7 and that of hydrogen is 1. Thus the molecular number of the ammonium cation can be calculated and compared to that of the sodium ion.

	Atomic number		Molecular number
$\text{NH}_4^+$	$7 + (4 \times 1)$	=	11
$\text{Na}^+$	11	=	11

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

In a biologically active molecule the replacement of an atom or a group of atoms by another one presenting the same physiochemical properties is based on the concept of isosterism. The notion of isosterism was introduced in 1919 by **Langmuir** who was mainly focused in the similarities of electronic and steric arrangement of atoms, groups, radicals, and molecules.

The concept of isosters was then broadened by **Grimm** in 1925 with the statement of Hydride Displacement Law, and, further on, **Erlenmeyer** extended Grimm's classification defining isosters as atoms, ions, and molecules in which the peripheral layers of electrons can be considered identical. The extensive application of isosterism to modify a part of a biologically active molecule to get another one of similar activity, has given rise to the term of bioisosterism or non-classical isosterism. As initially defined by Friedman, bioisosters include all atoms and molecules which fit the broadest definition for isosters and that elicit the similar biological activity. In medicinal chemistry, **the concept of bioisosterism is a research tool of the utmost importance widely used in analogs design.**

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

In 1919 **Langmuir** first developed the concept of chemical isosterism to describe the similarities in physical properties among atoms, functional groups, radicals, and molecules. The similarities among atoms described by Langmuir primarily resulted from the fact that these atoms contained the same number of valence electrons and came from the same columns within the periodic table. This concept was limited to elements in adjacent rows and columns, inorganic molecules, ions, and small organic molecules, such as diazomethane and ketene.

To account for similarities between groups with the same number of valence electrons but different numbers of atoms. **Grimm** developed his hydride displacement law. This is not a "law" in the strict sense but, rather, more an illustration of similar physical properties among closely related functional groups. Descending diagonally from left to right in the table, hydrogen atoms are progressively added to maintain the same number of valence electrons for each group of atoms within a column. Within each column, the groups are considered to be "pseudoatoms" with respect to one another. This early view of isosterism did not consider the actual location, motion, and resonance of electrons within the orbitals of these functional group replacements.

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

Table 2.7. Comparison of Physical Properties of N<sub>2</sub>O and CO<sub>2</sub>

Property	N <sub>2</sub> O	CO <sub>2</sub>
Viscosity at 20°C	148 × 10 <sup>-6</sup>	148 × 10 <sup>-6</sup>
Density of liquid at 10°C	0.856	0.858
Refractive index of liquid, D line 16°C	1.193	1.190
Dielectric constant of liquid at 0°C	1.583	1.582
Solubility in alcohol at 15°C	3.250	3.130

Table 2.8. Grimm's Hydride Displacement "Law"

C	N	O	F	Ne
	CH	NH	OH	FH
		CH <sub>2</sub>	NH <sub>2</sub>	OH <sub>2</sub>
			CH <sub>3</sub>	NH <sub>3</sub>

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

Independently from **Allen, Langmuir** in 1919 defined the concept of isosterism:

***"Comolecules are thus isosteric if they contain the same number and arrangement of electrons. The comolecules of isosteres must, therefore, contain the same number of atoms. The essential differences between isosteres are confined to the charges on the nuclei of the constituent atoms."***

On the basis of these similarities, Langmuir identified a list of 21 groups of isosteres. He further deduced from the octet theory that the number and arrangement of electrons in these molecules are the same. Thus, isosteres were initially defined as those compounds or groups of atoms that have the same number and arrangement of electrons. Then, he defined other relationships in a similar manner. Argon was viewed as an isostere of  $K^+$  ion and methane as an isostere of  $NH_4^+$  ion. He deduced that  $K^+$  ions and  $NH_4^+$  ions must be similar because argon and methane are very similar in physical properties. The biological similarity of molecules such as  $CO_2$  and  $N_2O$  was later coincidentally acknowledged as both compounds were capable of acting as reversible anesthetics to the slime mold *Physarum polycephalum*.

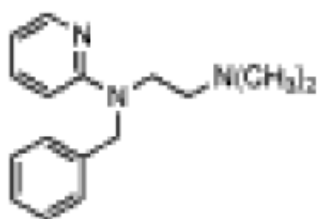
# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

**TABLE 15.1** Groups of Isosteres as Identified by Langmuir

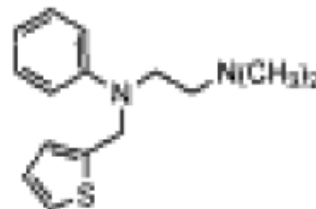
Groups	Isosteres
1	$\text{H}^-$ , He, $\text{Li}^+$
2	$\text{O}^{2-}$ , $\text{F}^-$ , Ne, $\text{Na}^+$ , $\text{Mg}^{2+}$ , $\text{Al}^{3+}$
3	$\text{S}^{2-}$ , $\text{Cl}^-$ , Ar, $\text{K}^+$ , $\text{Ca}^{2+}$
↓	↓
8	$\text{N}_2$ , CO, $\text{CN}^-$
9	$\text{CH}_4$ , $\text{NH}_4^+$
10	$\text{CO}_2$ , $\text{N}_2\text{O}$ , $\text{N}^{3+}$ , $\text{CNO}^-$
↓	↓
21	$\text{SeO}_4^{2-}$ , $\text{AsO}_4^{3-}$

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

Instead of considering only partial structures. **Hinsberg applied the concept of isomerism to entire molecules.** He developed the concept of "**ring equivalents**" — that is groups that can be exchanged for one another in aromatic ring systems without drastic changes in physicochemical properties relative to the parent structure. Benzene, thiophene, and pyridine illustrate this concept. A -CH=CH- group in benzene is replaced by the divalent sulfur -S- in thiophene, and a -CH= is replaced by the trivalent -N= to give pyridine. The physical properties of benzene and thiophene are very similar. For example, the boiling point of benzene is 81.1 °C, and that of thiophene is 84.4°C. Pyridine, however, deviates, with a boiling point of 115 °C. **Hinsberg therefore concluded that divalent sulfur (-S- or thioether) must resemble -C=C- in shape,** and these groups were considered to be isosteric. Note that hydrogen atoms are ignored in this comparison. Today this isosteric relationship is seen in many drugs.



Tripelennamine



Methaphenilene

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

**TABLE 15.2** Hydride Displacement Law: In Each Vertical Column the Atom is Followed by its Pseudoatoms

Number of electrons					
6	7	8	9	10	11
C <sup>4-</sup>	N <sup>3-</sup>	—O—	—F	Ne	Na <sup>+</sup>
	CH <sup>3-</sup>	—NH—	—OH	FH	
		—CH <sub>2</sub> —	—NH <sub>2</sub>	OH <sub>2</sub>	
			—CH <sub>3</sub>	NH <sub>3</sub>	OH <sub>3</sub> <sup>+</sup>
				CH <sub>4</sub>	NH <sub>4</sub> <sup>+</sup>

**TABLE 15.3** The Sulphur Atom is Approximately Equivalent to an Ethylenic Group (Size, Mass, Capacity to provide an Aromatic Lone Pair)

$M_{(-CH=CH-)} = 26$ 
 $M_{(S)} = 32$

Compound	E°C	Isostere	E°C
Benzene	80°	Thiophene	84°
Methylbenzene	110°	2-Methyl-thiophene	113°
Chlorobenzene	132°	2-Chloro-thiophene	130°
Acetylbenzene	200°	2-Acetyl-thiophene	214°



# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

It is difficult to relate biological properties to physicochemical properties of individual atoms, functional groups, or entire molecules, because many physicochemical parameters are involved simultaneously and, therefore, are difficult to quantitate. Simple relationships as described above often do not hold up across the many types of biological systems seen with medicinal agents. *That is what may work as an isosteric replacement in one biological system may not work in another system.* Because of this, it was necessary to introduce the term "**bioisosterism**" to describe functional groups related in structure and having similar biological effects. **Friedman** introduced the term bioisosterism and defined it as follows: "**Bioisosteres are (functional) groups or molecules that have chemical and physical similarities producing broadly similar biological properties**".

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

Recently, **Burger** expanded this definition to take into account biochemical views of biological activity:

*"Bioisosters are compounds or groups that possess near equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties such as hydrophobicity. Bioisosteric compounds affect the same biochemically associated systems as agonist or antagonists and thereby produce biological properties that are related to each other."*

Table 2.9. Classical Bioisosteres (Groups Within the Row Can Replace Each Other)

---

Monovalent bioisosteres

F, H  
 OH, NH  
 F, OH, NH or CH<sub>3</sub> for H  
 SH, OH  
 Cl, Br, CF<sub>3</sub>

Divalent bioisosteres:

—C=S, —C=O, —C=NH, —C=C—

Trivalent atoms or groups:

— $\underset{\text{H}}{\text{C}}=$  , —N=  
 —P= , —As=

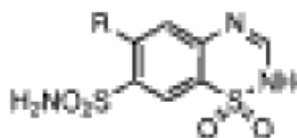
Tetrasubstituted atoms:

— $\overset{\oplus}{\text{N}}\text{—}$     — $\overset{\oplus}{\text{C}}\text{—}$     — $\overset{\oplus}{\text{P}}\text{—}$     — $\overset{\oplus}{\text{As}}\text{—}$

Ring equivalents:



# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM



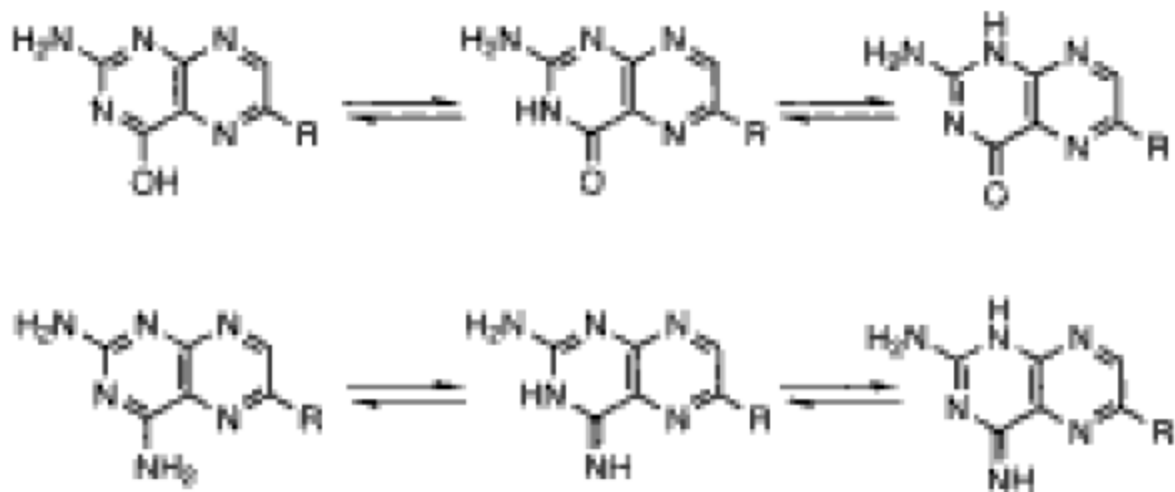
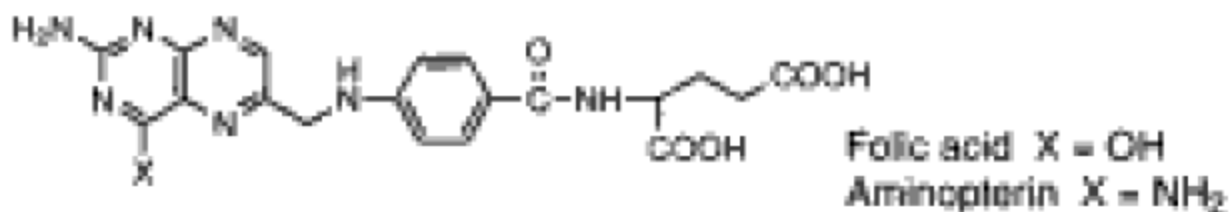
R =	Cl	Br	CF <sub>3</sub>
$\sigma$	+0.23	+0.23	+0.54
$\pi$	+0.71	+0.86	+0.88
$E_s$	-0.97	-1.16	-2.40

**Fig. 2.34.** Isosteric replacement of chlorine in thiazide diuretic: Comparison of physicochemical properties of the substituents.

**TABLE 15.4** Classic Bioisostere Atoms and Groups

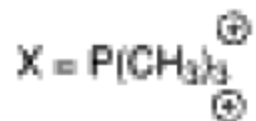
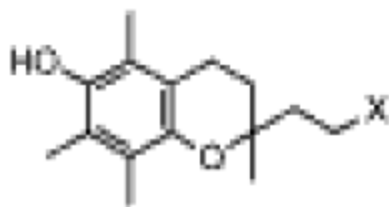
Monovalent	Divalent	Trivalent	Tetravalent
—OH, —NH <sub>2</sub> , —CH <sub>3</sub> , —OR	—CH <sub>2</sub> —	=CH—	=C=
—F, —Cl, —Br, —I, —SH, —PH <sub>2</sub>	—O—	=N—	=Si=
—Si <sub>3</sub> , —SR	—S—	=P—	=N <sup>+</sup> =
	—Se—	=As—	=P <sup>+</sup> =
	—Te—	=Sb—	=As <sup>+</sup> =
			=Sb <sup>+</sup> =

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM



**Fig. 2.35.** Isosteric replacement of OH by NH<sub>2</sub> in folic acid and possible tautomers of folic acid and aminopterin.

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM



$\alpha$ -Tocopherol  $X = \text{C}_{14}\text{H}_{29}$

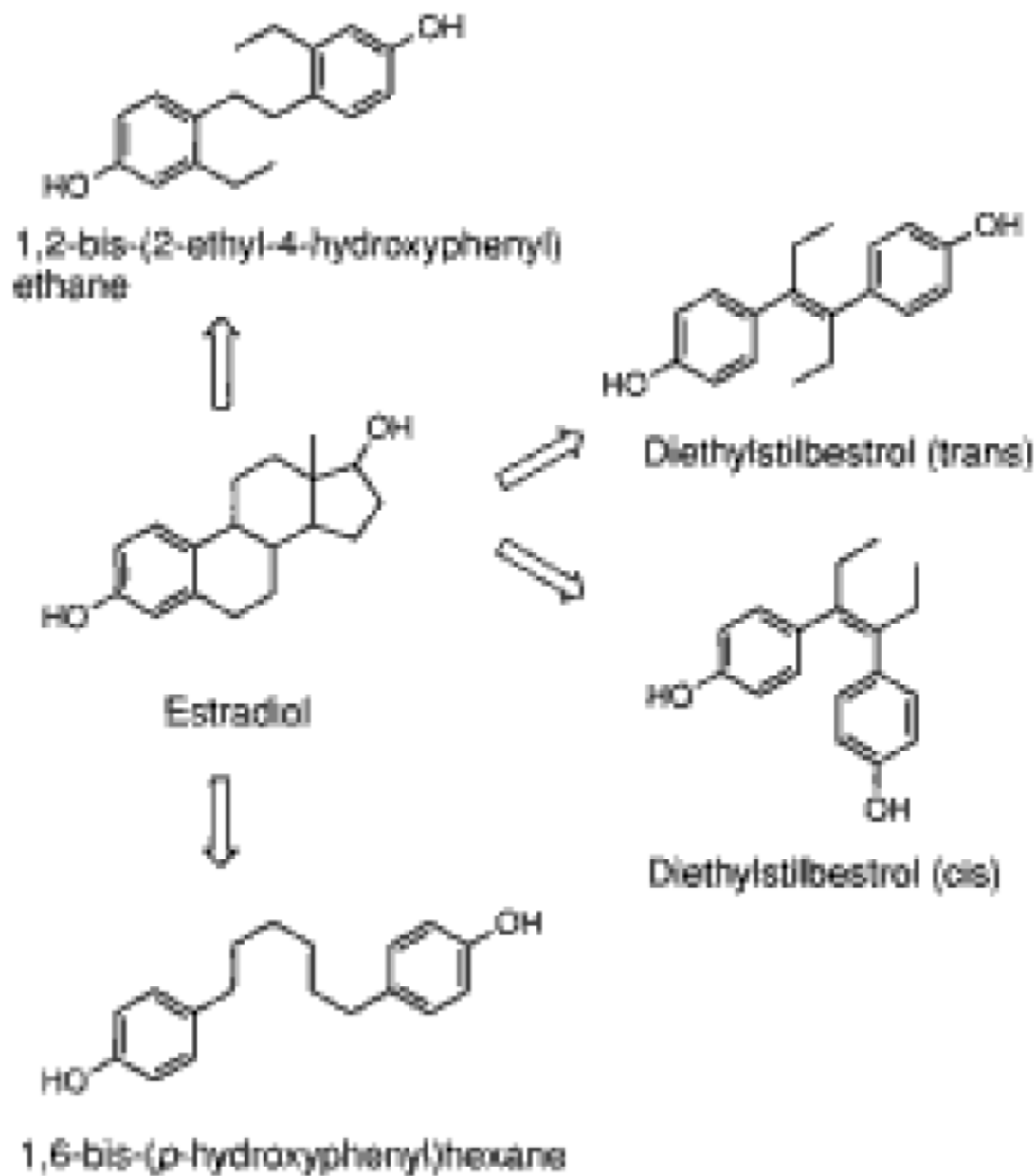
Tetravalent bioisosteres of  $\alpha$ -tocopherol.

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

**Nonclassical bioisosteres are replacements of functional groups not defined by classical definitions.** Some of these groups, however, mimic spatial arrangements, electronic properties, or some other physicochemical property of the molecule or functional group critical for biological activity. One example is the use of a double bond to position essential functional groups into a particular spatial configuration critical for activity.

The trans isomer of ***diethylstilbestrol*** has approximately the same potency as ***estradiol***, whereas the cis isomer is only one-fourteenth as active. In the trans configuration, the phenolic hydroxy groups mimic the correct orientation of the phenol and alcohol in estradiol.

Another example of a nonclassical replacement is that of a sulfonamide group for a phenol in catecholamines. With this example, steric factors appear to have less influence on receptor binding than acidity and hydrogen-bonding potential of the functional group on the aromatic ring. Both the phenolic hydroxyl of ***isoproterenol*** and the acidic proton of the ***arylsulfonamide*** have nearly the same pKa (~10). Both groups are weakly acidic and capable of losing a proton and interacting with the receptor as anions or participating as hydrogen-bond donors at the receptor.

**F**



# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

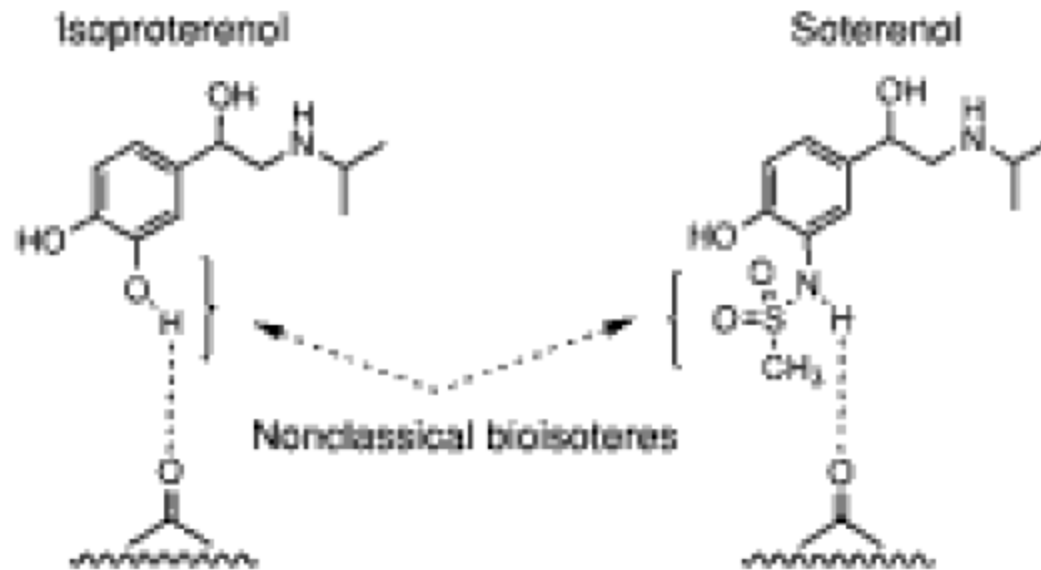


Fig. 2.38. Bioisosteric replacement of m-OH of isoproterenol with a sulfonamido group and similar hydrogen-bonding capacity to a possible drug receptor.

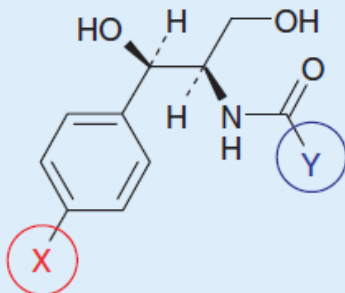
# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

**TABLE 15.5** Non-Classical Isosteres

—CO—	—COOH	—SO <sub>2</sub> NH <sub>2</sub>	—H	—CONH—	—COOR	—CONH <sub>2</sub>
—CO <sub>2</sub> —	—SO <sub>3</sub> H	—PO(OH)NH <sub>2</sub>	—F	—NHCO—	—ROCO—	—CSNH <sub>2</sub>
—SO <sub>2</sub> —	—tetrazole					
—SO <sub>2</sub> NR—	—SO <sub>2</sub> NHR —SO <sub>2</sub> NH <sub>2</sub>		—OH —CH <sub>2</sub> OH		—catechol	
—CON—	—3-hydroxyisoxazole				—benzimidazole	
—CH(CN)—	—2-hydroxychromones		—NHCONH <sub>2</sub>			C <sub>4</sub> H <sub>4</sub> S
R—S—R			—NH—CS—NH <sub>2</sub>			—C <sub>5</sub> H <sub>4</sub> N
(R—O—R)	≡N—					—C <sub>6</sub> H <sub>5</sub>
R—N(CN)—	C(CN)=R'		—NH—C(=CHNO <sub>2</sub> )—NH <sub>2</sub> —NH—C(=CHCN)—NH <sub>2</sub>			
—halide						—C <sub>4</sub> H <sub>4</sub> NH
	—CF <sub>3</sub>					
	—CN					
	—N(CN) <sub>2</sub>					
	—C(CN) <sub>3</sub>					

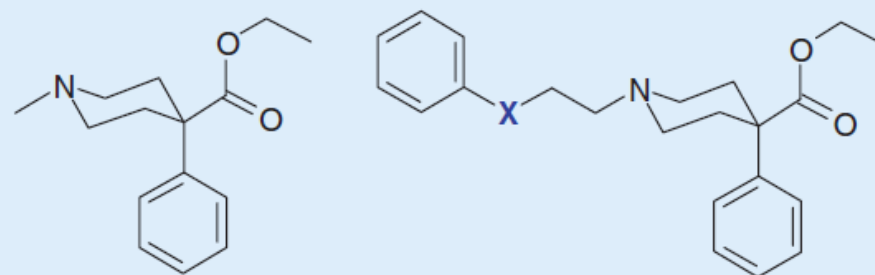
# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

**TABLE 15.6** Isosteric Replacements in the Amphenicol Family



Compound	X	Y
Chloramphenicol	—NO <sub>2</sub>	—CH—Cl <sub>2</sub>
Thiamphenicol	CH <sub>3</sub> —SO <sub>2</sub> —	—CH—Cl <sub>2</sub>
Cetophenicol	CH <sub>3</sub> —CO—	—CH—Cl <sub>2</sub>
Azidamphenicol	—NO <sub>2</sub>	—CH <sub>2</sub> —N <sub>3</sub>

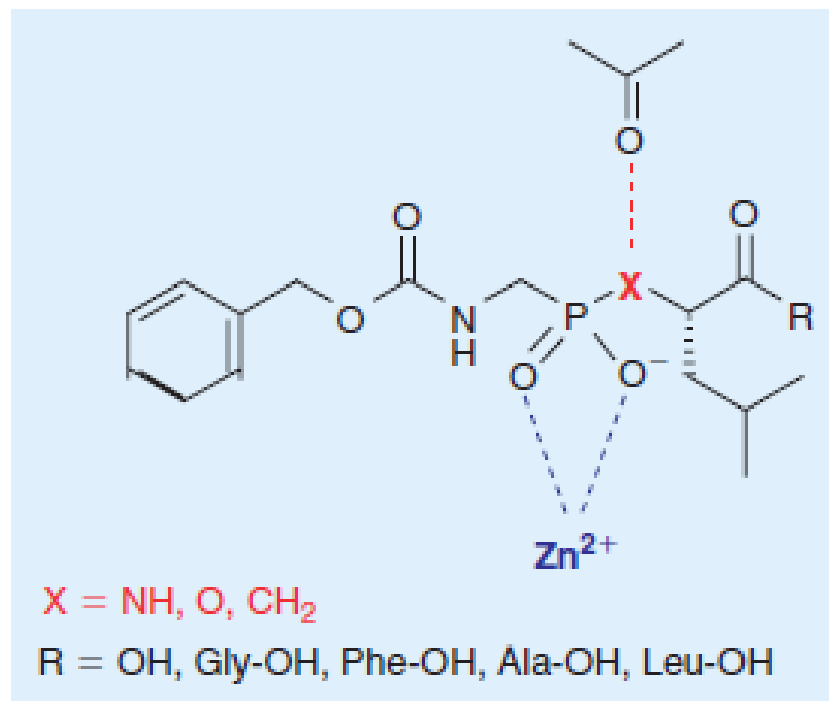
**TABLE 15.7** Meperidine Analogs[17]



Meperidine

X	Analgesic potency (Meperidine = 1)
O	12
NH	80
CH <sub>2</sub>	20
S	1,5

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM



**FIGURE 15.6** Isostery in thermolysin inhibitors.<sup>19</sup>

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

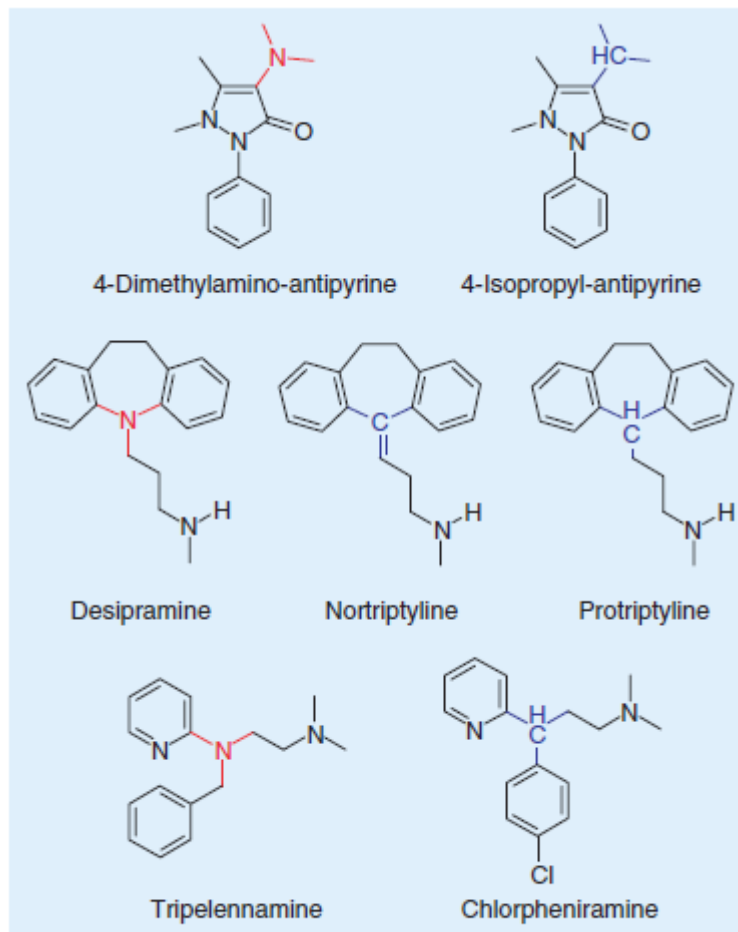
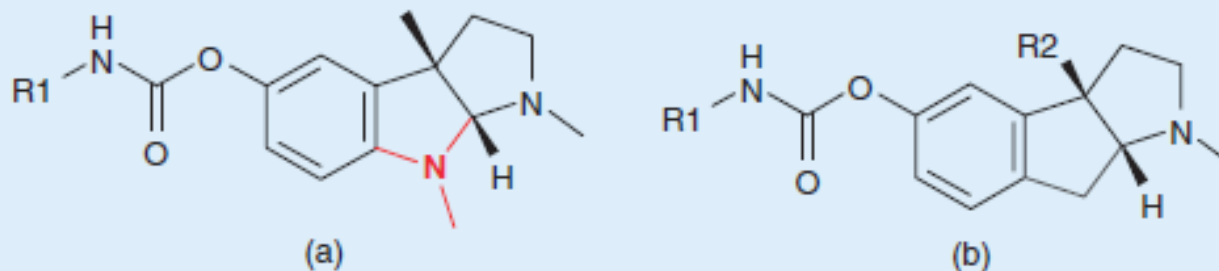


FIGURE 15.7 Interchange of trivalent atoms and groups.

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

TABLE 15.8 Physostigmines (a) and Carba-isosteres (b)<sup>20</sup>



Compound	R1	R2	IC <sub>50</sub> (nM)	LD <sub>50</sub> (mg/kg)
(-)-Physostigmine	CH <sub>3</sub>	CH <sub>3</sub>	128	0.88
(-)-Heptyl physostigmine	n-C <sub>7</sub> H <sub>13</sub>	CH <sub>3</sub>	110	24
(±)-Carba-isostere 1	n-C <sub>7</sub> H <sub>13</sub>	CH <sub>3</sub>	114	21
(-)-Carba-isostere 2a	n-C <sub>7</sub> H <sub>13</sub>	C <sub>2</sub> H <sub>5</sub>	36	6
(+)-Carba-isostere 2b	n-C <sub>7</sub> H <sub>13</sub>	C <sub>2</sub> H <sub>5</sub>	211	18

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

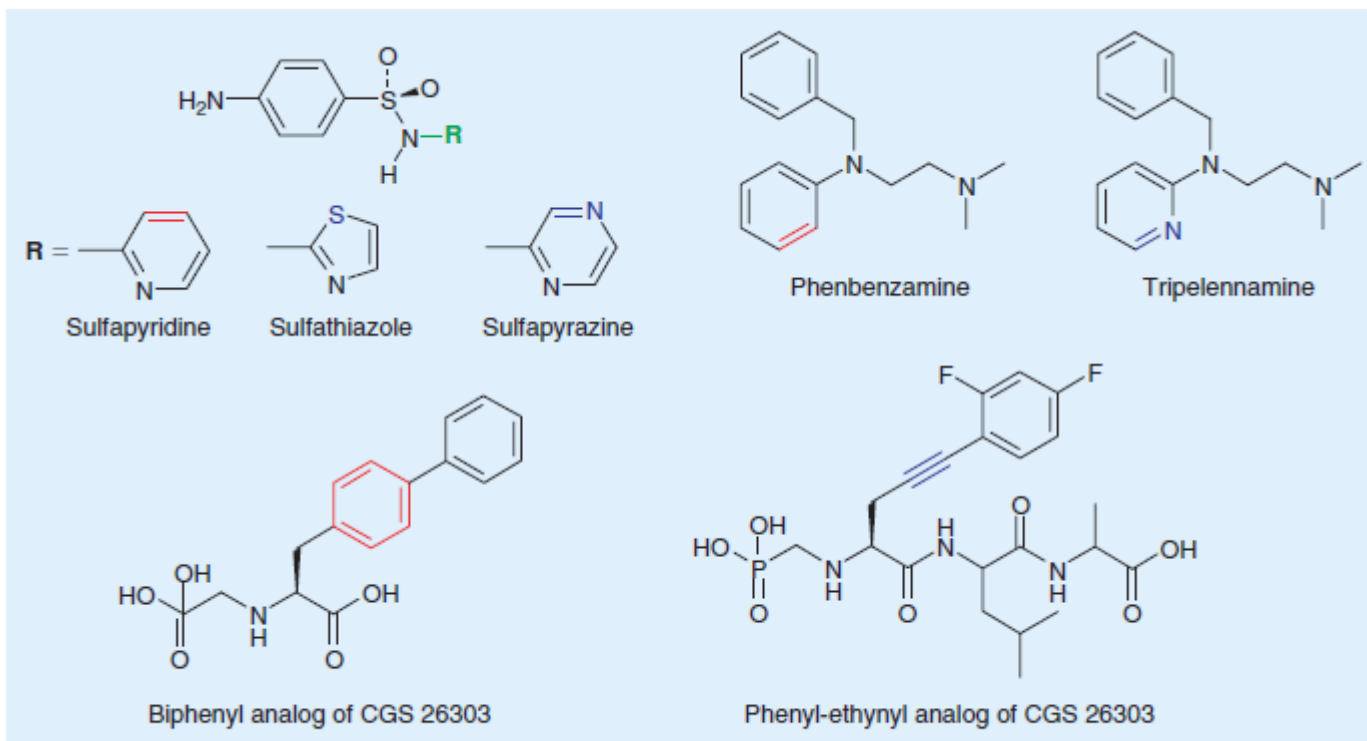
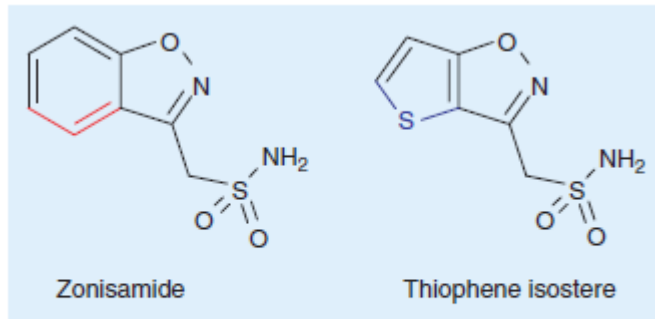
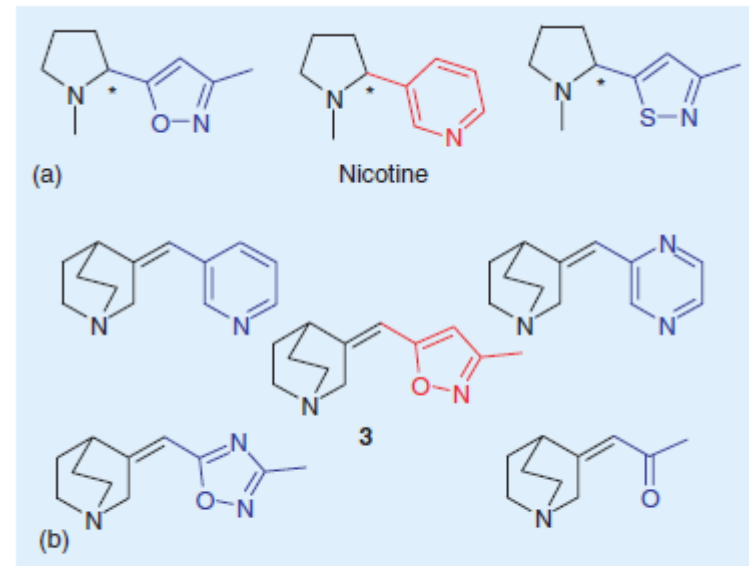


FIGURE 15.8 Classical ring equivalents.

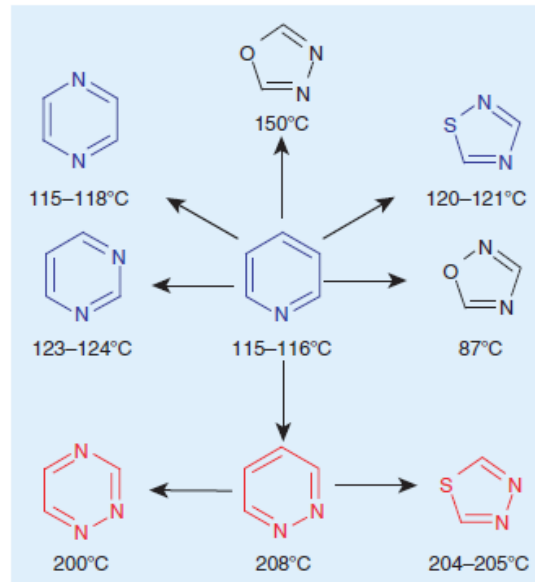
# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM



**FIGURE 15.9** The thiophene isostere of zonisamide is practically inactive as an anticonvulsant.



**FIGURE 15.10** Ligands for central cholinergic receptors with different non-classical bioisosteres of the pyridine ring.



**FIGURE 15.16** Structures and boiling points of pyridine and pyridazine isosteres.



# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

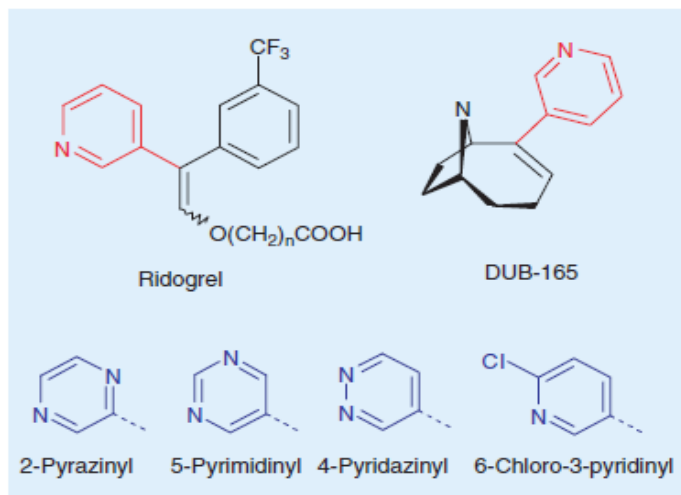


FIGURE 15.11 Bioisosteric moieties for the 3-pyridyl ring.

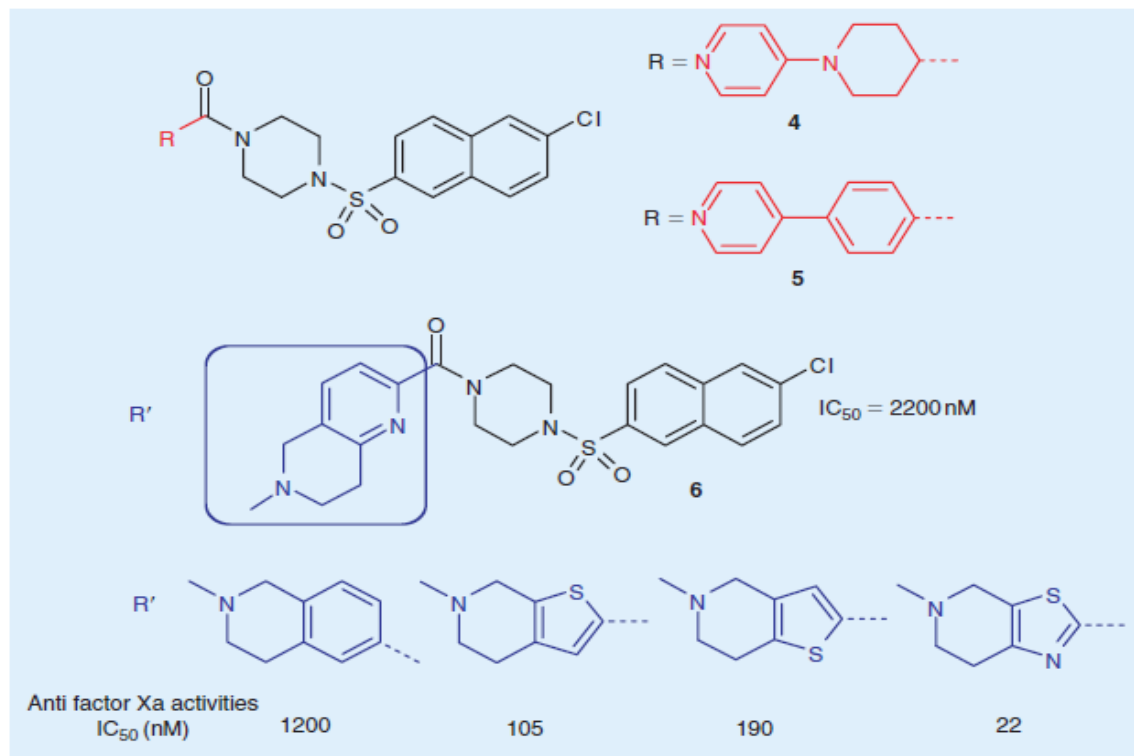
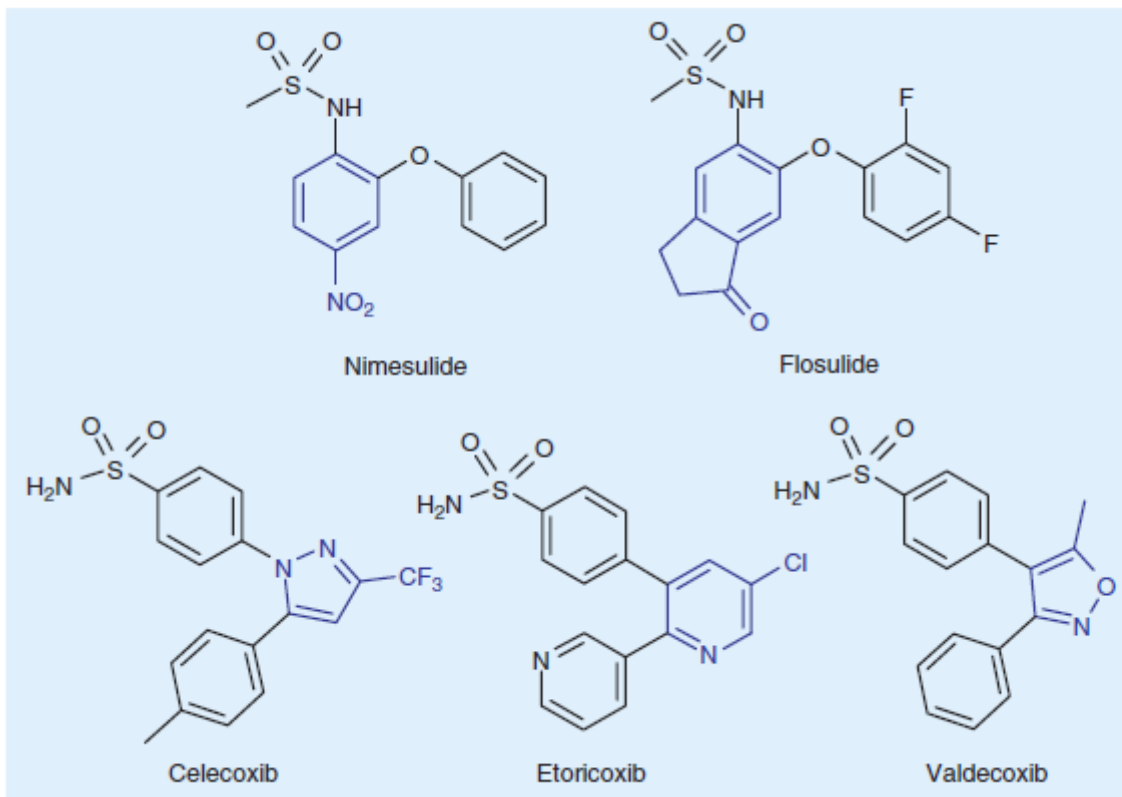


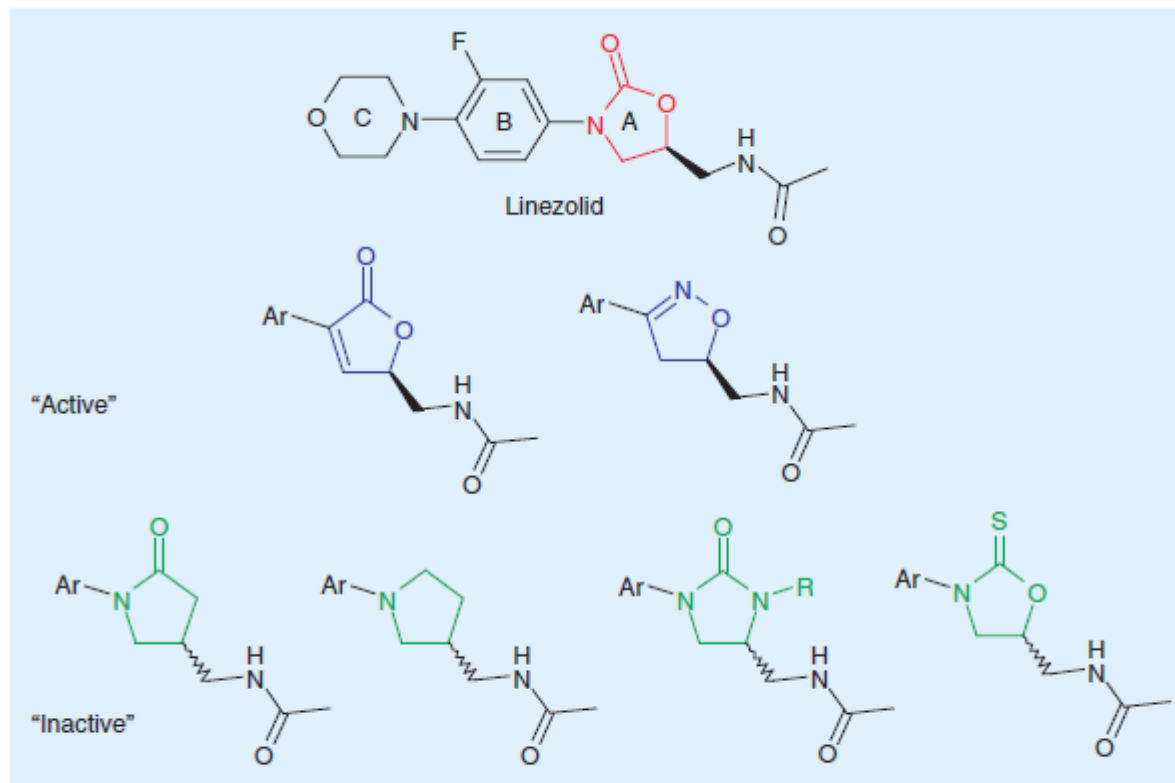
FIGURE 15.12 Bioisosteric replacements of the pyridine ring in a series of factor Xa inhibitors.

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM



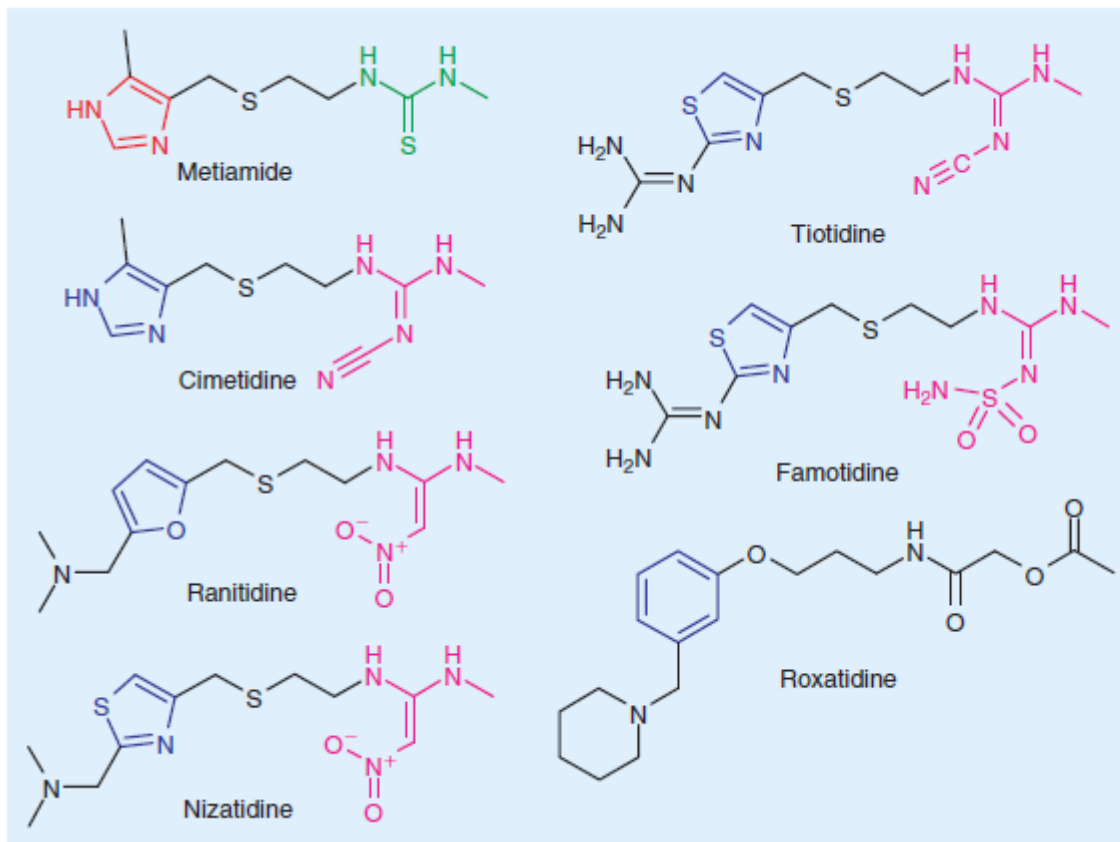
**FIGURE 15.17** Examples of selective cyclooxygenase-2 inhibitors showing different ring equivalents.

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM



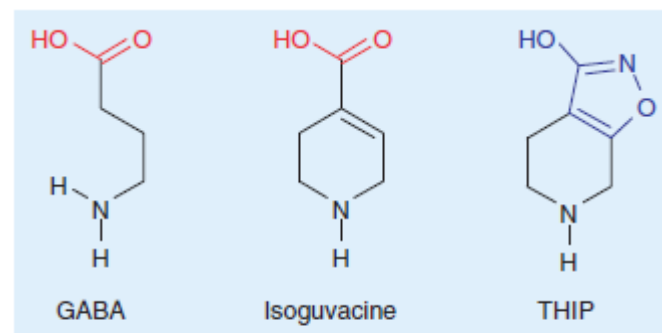
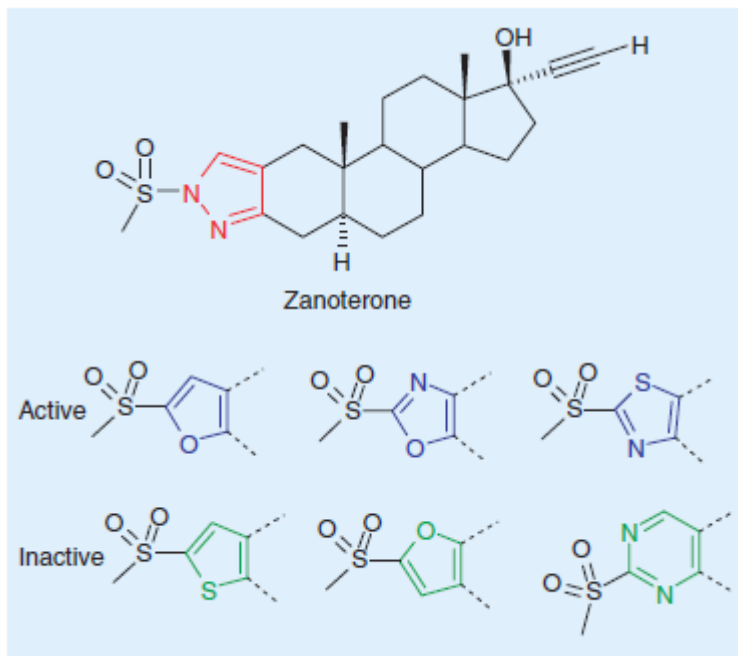
**FIGURE 15.18** Oxazolidinone bioisosteres synthesized as antibacterial agents.

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM



**FIGURE 15.19** Antiulcer H<sub>2</sub>-receptor histamine antagonists: evolution of structures in the course of the time. Note the progressive use of a furan, a thiazole, and finally a phenyl ring in place of the original imidazole ring. On the same series it is noteworthy the bioisosterism of the urea moiety with different surrogates: thiourea, *N*-cyanoguanidine, *N*-nitro-ethene diamine, and *N*-aminosulfonil guanidine.

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM



**FIGURE 15.21** An example of bioisosterism, or non-classical isosterism: GABA, isoguvacine, and THIP are all agonists for the GABA-A receptor. The 3-hydroxy-isoxazole ring has a comparable acidity to that of a carboxylic acid function.<sup>57</sup>

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

**TABLE 15.11** Carboxylic Acid Isosteres: Direct Derivatives

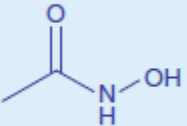
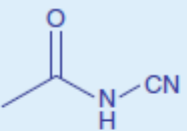
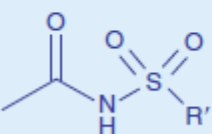
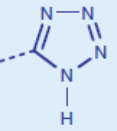
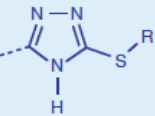
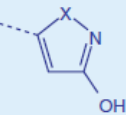
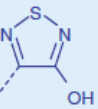
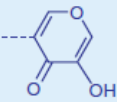
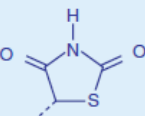
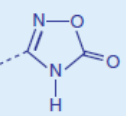
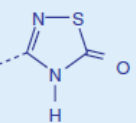
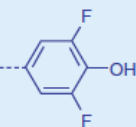
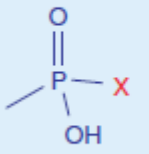
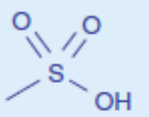
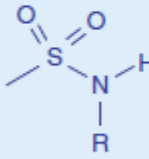
	Hydroxamic acids	High chelating power Histone deacetylase inhibitors Matrix metalloproteinases inhibitors Tumor necrosis factor $\alpha$ converting enzyme	Almquist <i>et al.</i> <sup>58</sup> Massa <i>et al.</i> , <sup>59</sup> Lu <i>et al.</i> <sup>60</sup> Remiszewski <i>et al.</i> , <sup>61</sup> Plumb <i>et al.</i> , <sup>62</sup> Kelly <i>et al.</i> , <sup>63</sup> Buggy <i>et al.</i> <sup>64</sup> Hanessian <i>et al.</i> <sup>65</sup> Aranapakam <i>et al.</i> <sup>66,67</sup> Noe <i>et al.</i> <sup>68</sup> Duan <i>et al.</i> <sup>69</sup>
	Acyl-cyanamides	Mainly academic interest	von Kohler <i>et al.</i> <sup>70</sup> Kwon <i>et al.</i> <sup>71</sup>
	Acyl-sulfonamides	Glycine, GABA, and $\beta$ -alanine analogs Antiatherosclerotics pK <sub>a</sub> # 4,5 $\beta_3$ Adrenergic receptor agonist hepatitis C virus	Drummond and Johnson <sup>72</sup> Albright <i>et al.</i> <sup>73</sup> Uehling <i>et al.</i> <sup>74</sup> Johansson <i>et al.</i> <sup>75</sup>

TABLE 15.12 Carboxylic Acid Isosteres: Planar Acidic Heterocycles and Aryl Derivatives

	Tetrazoles	Very popular, great number of publications. $pK_a = 6.6$ to $7.2$	Bovy <i>et al.</i> <sup>88</sup> Marshall <i>et al.</i> <sup>89</sup>
	Mercaptoazoles + Sulfinylazoles + Sulfonylazoles	Phosphonate isosteres $pK_a$ mercapto: $8.2$ – $11.5$ $pK_a$ sulfinyl: $5.2$ – $9.8$ $pK_a$ sulfonyl: $4.8$ – $8.7$	Chen <i>et al.</i> <sup>20</sup>
  X = O or S	Isoxazoles Isothiazoles	GABA and glutamic acid analogs	Krogsgaard-Larsen <i>et al.</i> <sup>57</sup> Krogsgaard-Larsen <sup>90</sup>
	Hydroxy-thiadiazole	Isoxazole isostere $pK_a \# 5$	Lunn <i>et al.</i> <sup>91</sup>
	Hydroxy-chromones	Kojic acid derivatives (as GABA agonists)	Atkinson <i>et al.</i> <sup>92</sup>
	Thiazolidinediones	Dual PPAR $\alpha/\gamma$ agonists	Hulin <i>et al.</i> , <sup>93</sup> Henke <sup>94</sup>
	1,2,4-Oxadiazole-5(4H)-ones	Antimycobacterial	Cezginci <i>et al.</i> <sup>95</sup>
	1,2,4-Thiadiazole-5(4H)-ones	Antimycobacterial	Cezginci <i>et al.</i> <sup>95</sup>
	3,5-Difluoro-4-hydroxyphenyl	Aldose reductase inhibitor GABA analog	Nicolaou <i>et al.</i> <sup>96</sup> Qiu <i>et al.</i> <sup>97</sup>

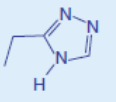
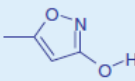
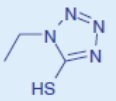
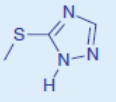
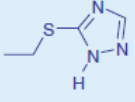
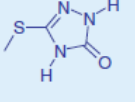
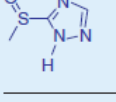
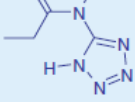
# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

**TABLE 15.13** Carboxylic Acid Isosteres: Non Planar Sulfur- or Phosphorus-Derived Acidic Functions

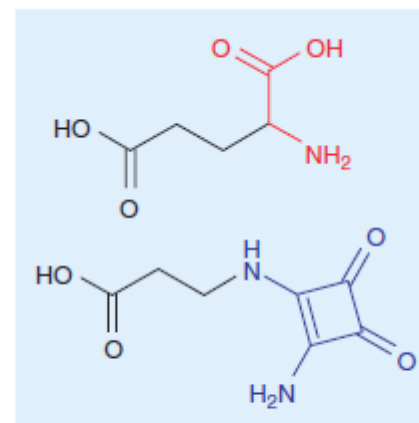
	<p>X = H X = OH X = NH<sub>2</sub> X = CH(OR)<sub>2</sub></p>	<p>Phosphinates Phosphonates Phosphonamides</p>	<p>Many examples in glutamate and in GABA<sub>B</sub> antagonist series</p>	<p>Froestl <i>et al.</i><sup>112</sup></p>
		<p>Sulfonates</p>	<p>Sulphonic analogs of GABA and glutamic acid</p>	<p>Rosowski <i>et al.</i><sup>113</sup></p>
		<p>Sulfonamides</p>	<p>Weak acids, used rather as equivalents of phenolic hydroxyls in the design of catecholamine analogs</p>	<p>von Kohler <i>et al.</i><sup>70</sup></p>



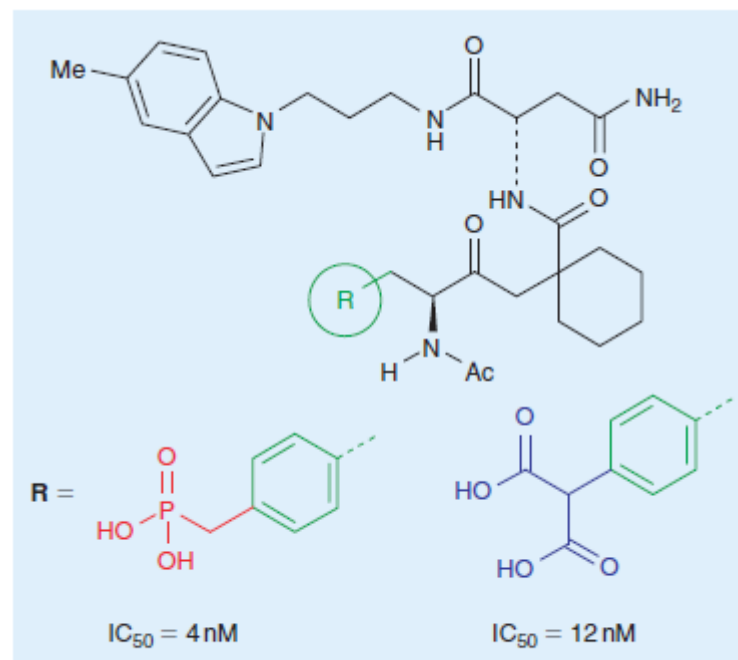
**TABLE 15.14** Exploration of the Carboxyl Isosterism Possibilities in a Series of CCK Antagonists.

R	IC <sub>50</sub> (nM) CCK-B	IC <sub>50</sub> (nM) CCK-A	A/B ratio	pK <sub>a</sub>
R-CH <sub>2</sub> -COOH	1.7	4500	2500	5.6
<b>Charge distributed monoanionic acid mimics</b>				
	6.0	970	160	5.4
	2.6	1700	650	6.5
	2.4	620	260	4.3
	2.5	680	270	>9.5
	16	850	53	>9.5
	4.3	660	150	7.7
	1.7	940	550	7.0
	6.3	1300	200	5.2

# GROUP MODIFICATION. ND I



**FIGURE 15.25** 3,4-Diamino-3-cyclobutene-1,2-dione as surrogate of the  $\alpha$ -amino carboxylic acid function.



**FIGURE 15.26** Malonates as surrogates of phosphonates.

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

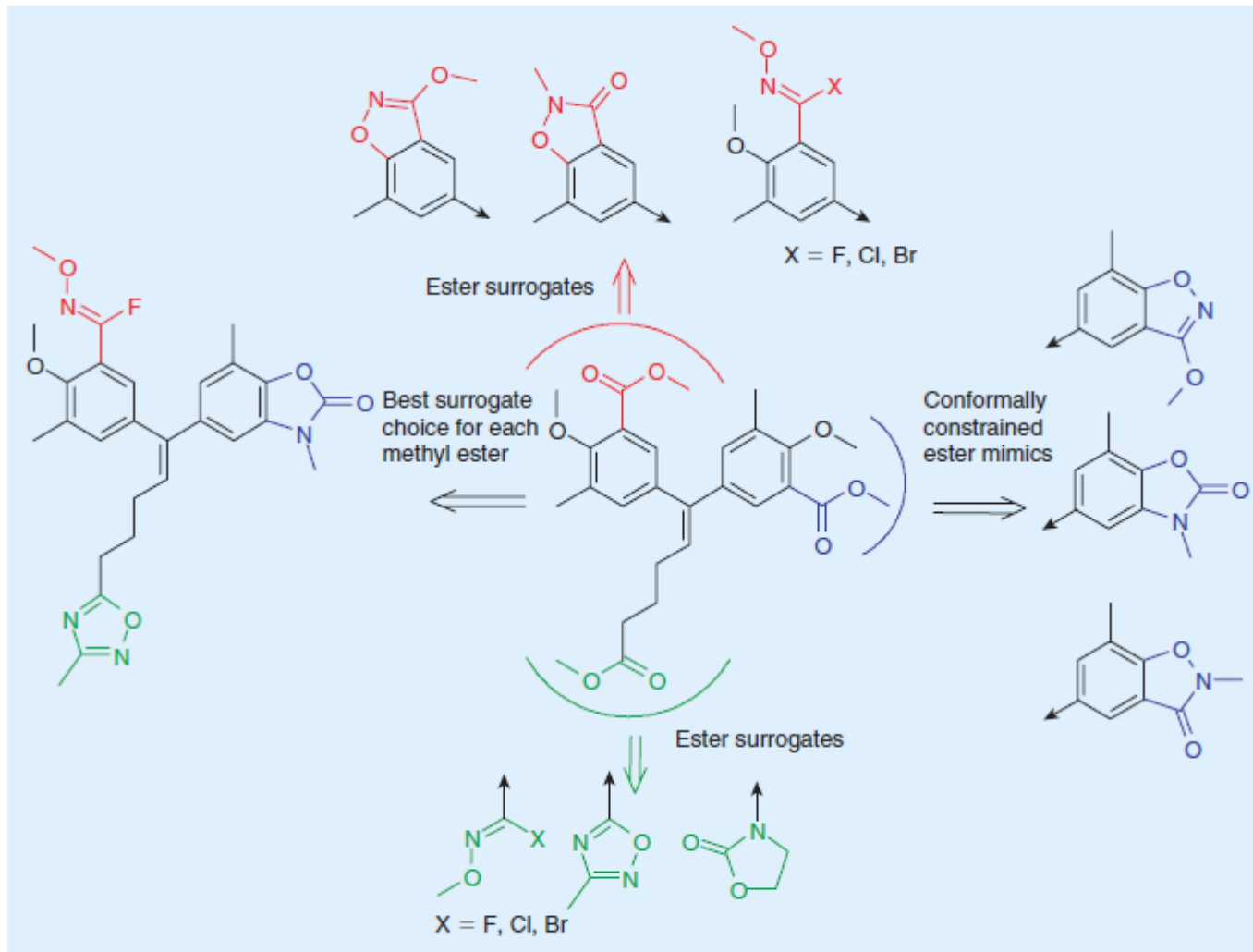
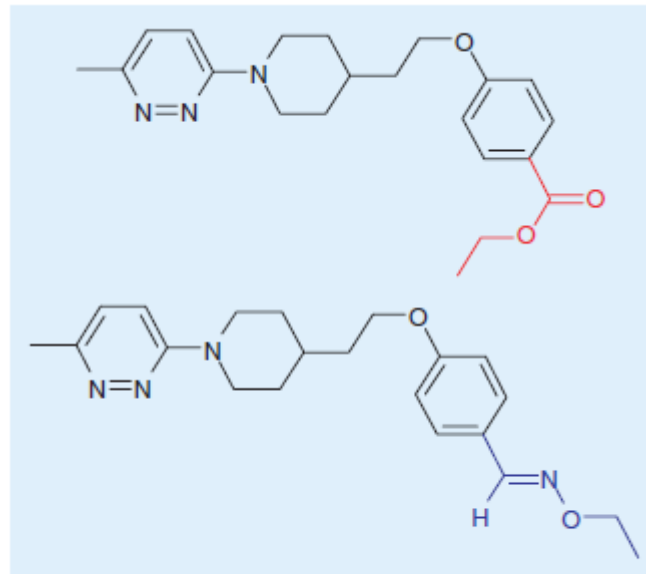


FIGURE 15.29 Design of new metabolically stable HIV inhibitor.

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM



**FIGURE 15.30** Ethyl oxime ether as ester replacement gave an improved bioavailability.

# FUNCTIONAL GROUP MODIFICATION.

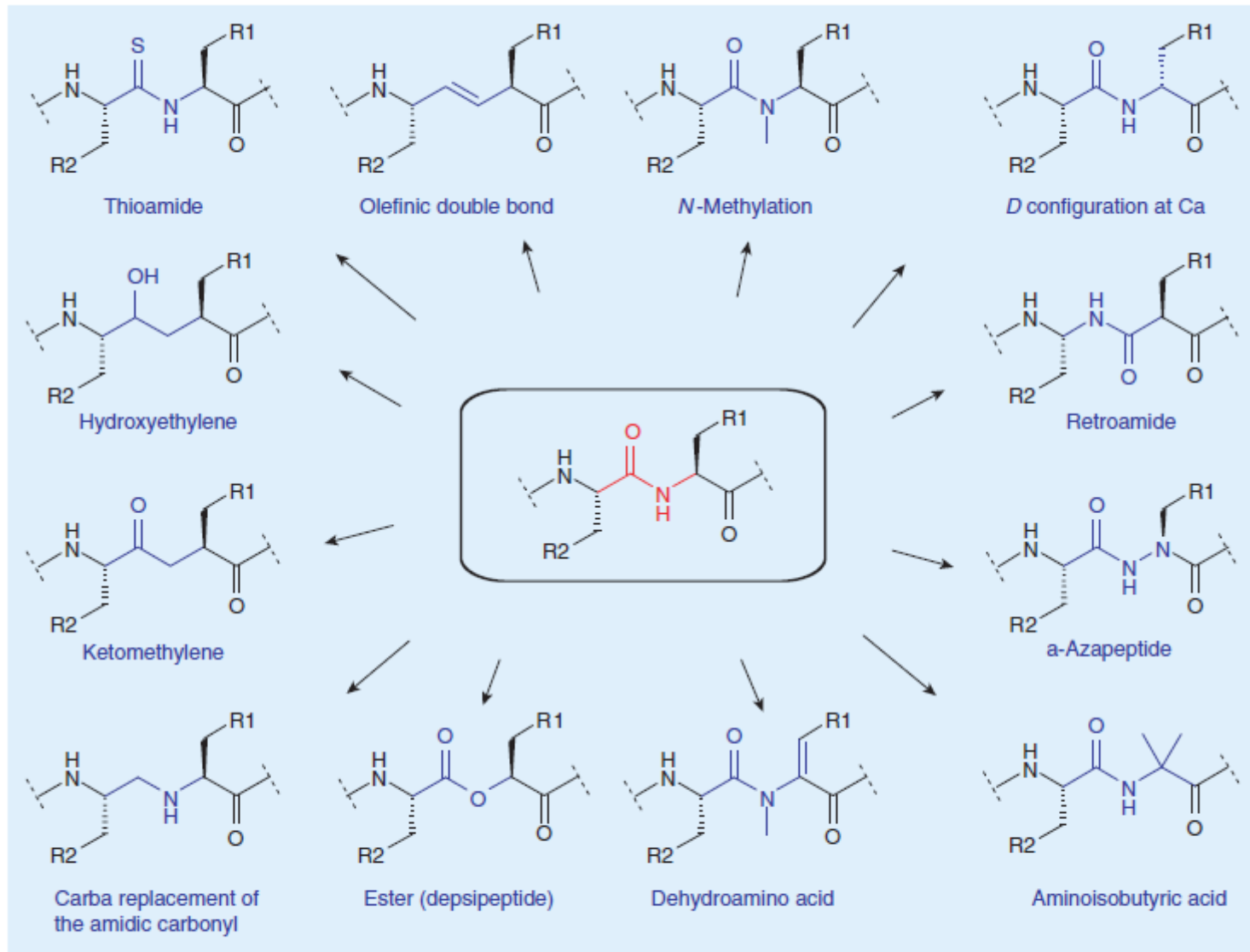


FIGURE 15.33 Well-established isosteric replacements for peptidic bonds.

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

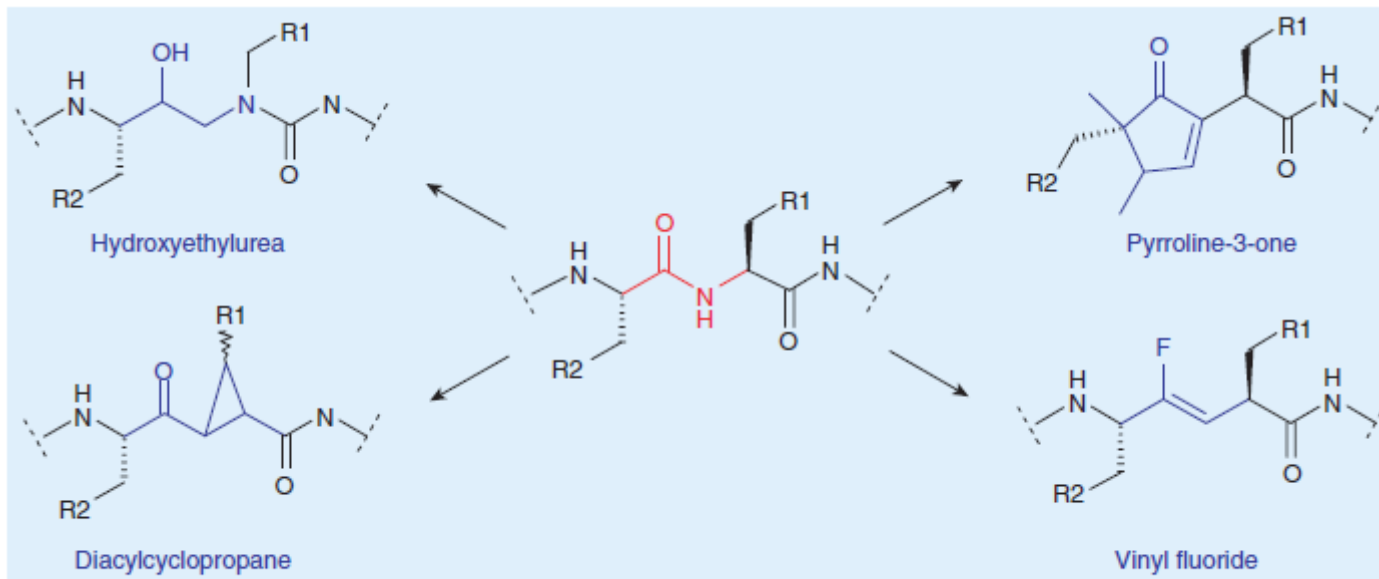
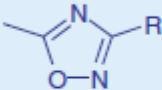
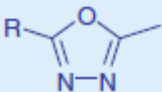
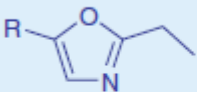
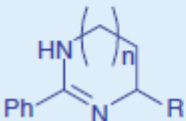
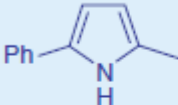
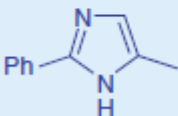


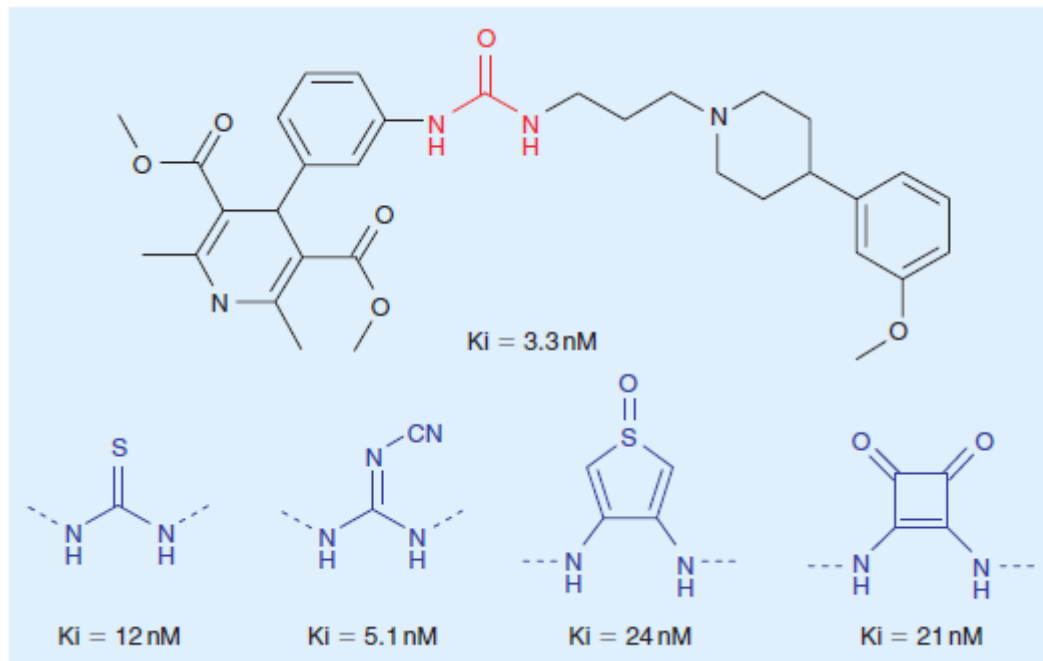
FIGURE 15.34 Unusual isosteric replacements for the peptidic bond.

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

**TABLE 15.15** Heterocyclic Surrogates of the Amide Bond

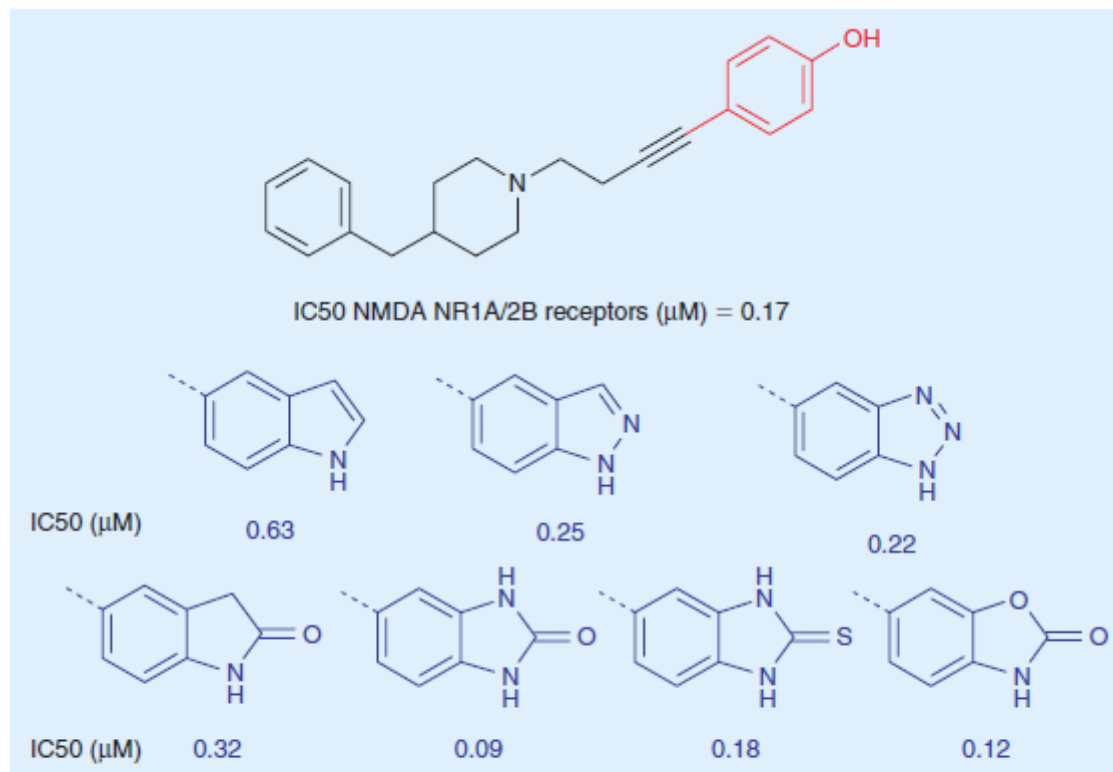
	1,2,4-Oxadiazoles	$\beta_3$ adrenergic receptor agonist	Naylor <i>et al.</i> , <sup>157,158</sup> Feng <i>et al.</i> , <sup>156</sup> Biftu <i>et al.</i> , <sup>155</sup> Parmee <i>et al.</i> <sup>159</sup>
		Fatty acid oxidation inhibitors	Elzein <i>et al.</i> , <sup>164</sup> Koltun <i>et al.</i> <sup>165</sup>
	1,3,4-Oxadiazoles	Phe-Gly peptidomimetics NK1 receptor antagonists	Borg <i>et al.</i> <sup>163</sup> Ladduwahetty <i>et al.</i> <sup>162</sup>
	Oxazoles	Fatty acid oxidation inhibitors	Elzein <i>et al.</i> , <sup>164</sup> Koltun <i>et al.</i> <sup>165</sup>
	Cyclic amidines	Dopamine D4 receptor agonists	Einsiedel <i>et al.</i> <sup>166,167</sup>
	Pyrroles	D3 antagonists	Einsiedel <i>et al.</i> <sup>168</sup>
	Phenylimidazoles	D4 receptor ligand	Thurkauf <i>et al.</i> <sup>169</sup>

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM



**FIGURE 15.37** Binding affinities for various urea bioisosteres acting as antagonists at the NPY Y<sub>1</sub> receptor.

# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM



**FIGURE 15.39** Bioisosteric replacements of the phenol function in the design of *N*-methyl-D-aspartate (NMDA) receptor antagonists.



# FUNCTIONAL GROUP MODIFICATION. ISOSTERISM AND BIOISOSTERISM

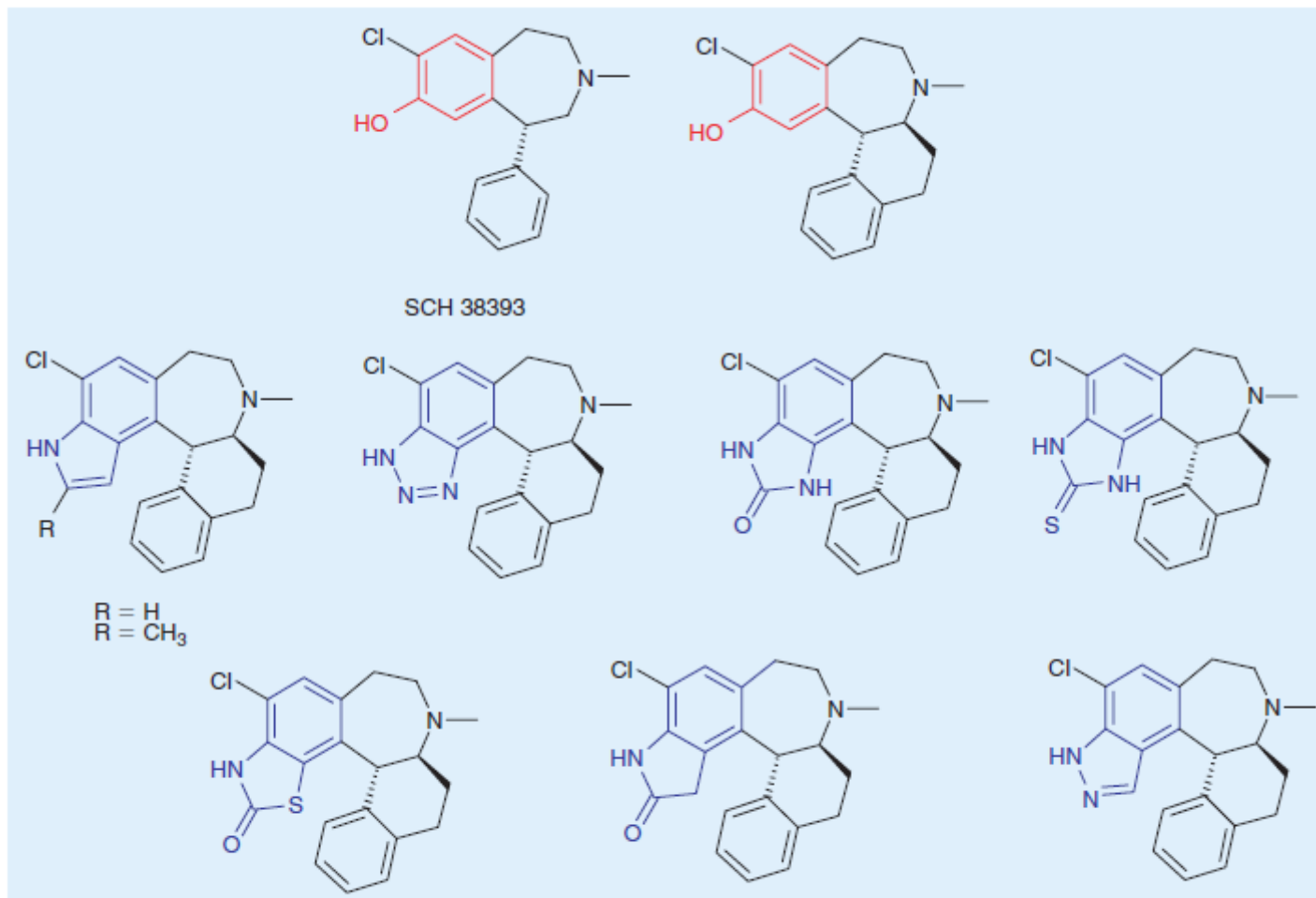
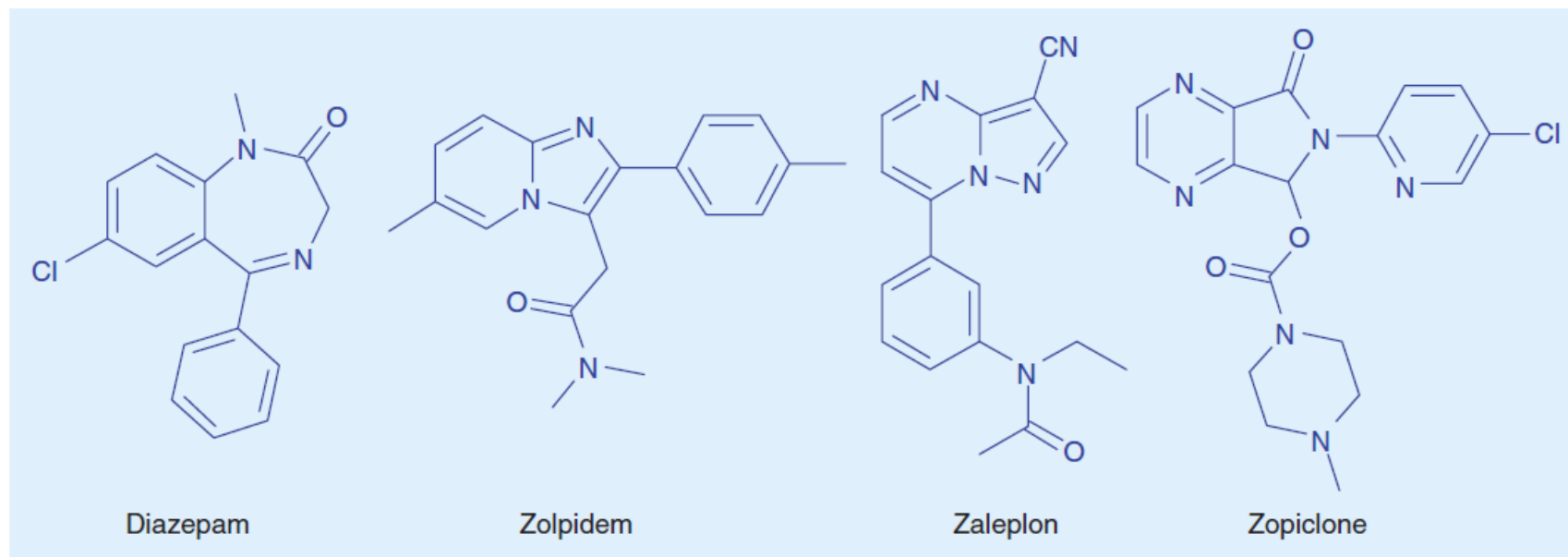


FIGURE 15.40 Phenol bioisosteres of benzazepine D<sub>1</sub>/D<sub>5</sub> antagonists.

# FUNCTIONAL GROUP MODIFICATION.

## Scaffold Hopping

*Taken in its broadest meaning, bioisosterism include the replacement of the initial molecular scaffold by a different one, keeping the same biological activity.* This approach, called **scaffold hopping**, is well illustrated by molecules like diazepam, zolpidem, zaleplon, and zopiclone which exert the same biological response acting as full agonists of GABA-A ( $\gamma$ -aminobutyric acid) receptor at the benzodiazepine site though being structurally different.



**FIGURE 15.3** Scaffold hopping can be considered as the broadest example of bioisosterism: structurally different molecules elicit the same biological activity.

# FUNCTIONAL GROUP MODIFICATION.

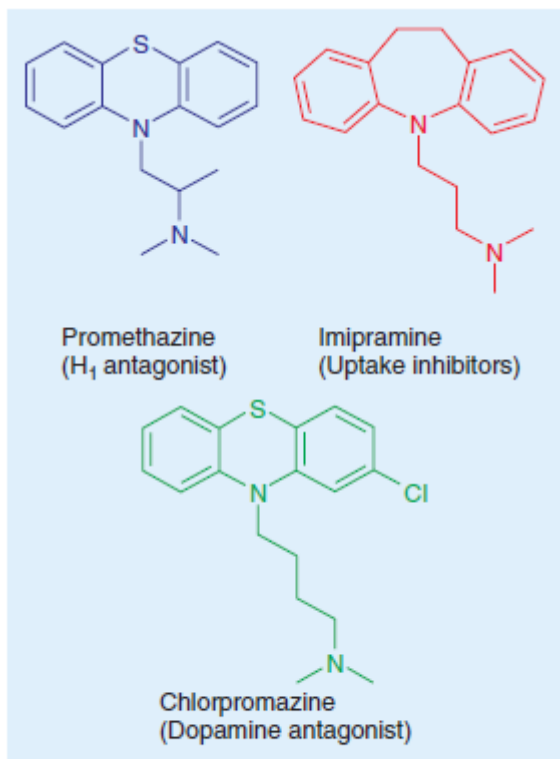
## Scaffold Hopping

***Scaffold hopping is a useful technique used by medicinal chemists to discover structurally novel compounds starting from known active molecules by changing the molecular backbone of the template.*** Medicinal chemists have quite often the need of "jumping" in a different chemical space: new chemical entities offer the choice of easier chemical accessibility and so possibility of speeding up the lead optimization process. Switching to a different molecular backbone can help to avoid some undesirable ADME-tox properties. Scaffold hopping come to a rescue also to move from complex natural molecules to easier synthesisable small molecules.

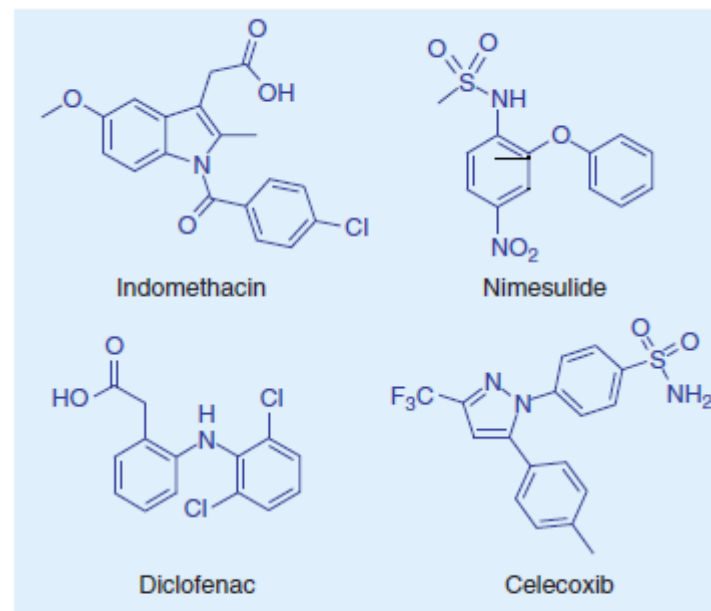
The concept of scaffold hopping relies upon the assumption that structurally and chemically distinct templates interact with the same receptor inducing equivalent biological activity. This seems to contradict the leading principle of the lead optimization process and drug design that is based on the concept that chemical similarity is reflected by similar biological activity. On the other hand this concept is not always true. In fact not always structural and chemical analogy predicts similar biological affinity. In fact promethazine, imipramine, and chlorpromazine that are strictly similar from a structure point of view, interact with different receptors and present complete different therapeutic profiles acting respectively as H1 antagonist, uptake inhibitor and dopamine antagonist.

# FUNCTIONAL GROUP MODIFICATION.

## Scaffold Hopping



**FIGURE 15.53** Structure and chemical similarity are not always synonymous of similar biologically active compounds.



**FIGURE 15.54** An example of scaffold hopping: four structurally different molecules have similar therapeutic properties by interacting with the same receptor.

# FUNCTIONAL GROUP MODIFICATION.

## Scaffold Hopping

**Indeed scaffold hopping can be interpreted as the broadest expansion of the bioisosterism concept.** The idea of scaffold hopping is indeed not new, it is rather a new term to designate known experimental evidences. A retrospective analysis of the marketed drugs and/or of the ligands acting on the same receptors brings up some interesting examples of structurally different molecules eliciting the same biological activity. A nice example is given by the non-steroidal antiinflammatory drugs (NSAIDs) COX-2 inhibitors.

Actually the GABA-A ligands at the benzodiazepine site give a nice picture of matching and mismatching of scaffold hopping and bioisosterism. Looking at diazepam, Zolpidem, zopiclone, and zaleplon, a structural analogy is barely found. Despite this they are all GABA-A ligands acting as full agonists. The same can be said about the inverse agonists DMCM, 16, 17, FG 8094, and 18: chemically different compounds have comparable biological activity. On the other hand similar compounds like FG 8094, Bretazenil, and Ro 15-1788, do not give the same biological response.

# FUNCTIONAL GROUP MODIFICATION. Scaffold Hopping

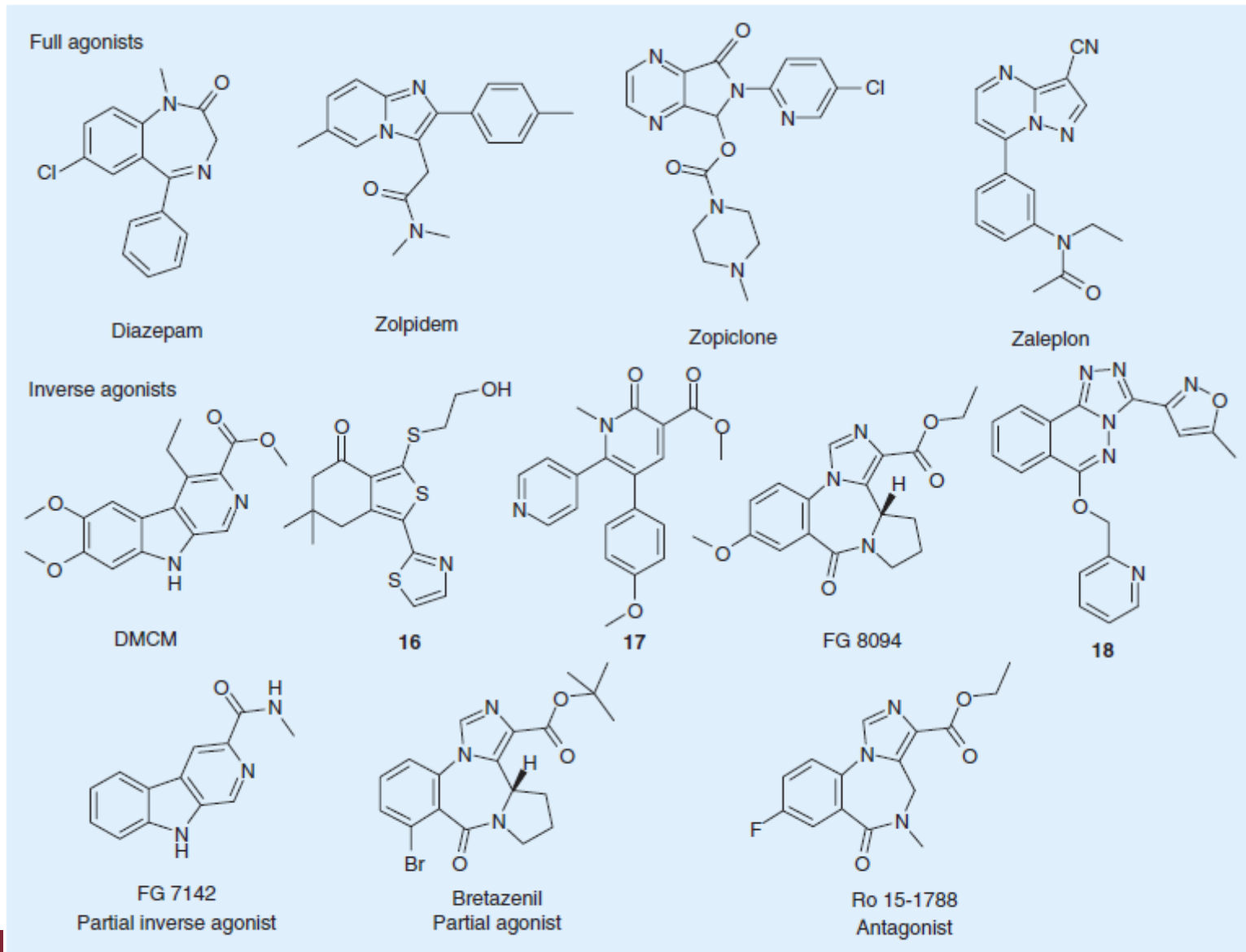


FIGURE 15.55 GABA-A ligands binding at benzodiazepine site.

# FUNCTIONAL GROUP MODIFICATION.

## Scaffold Hopping

The examples cited illustrated that similar biological activity can be obtained with structurally different molecules which seems to contradict the bioisosterism principle discussed. The serendipitous examples of scaffold hopping described have been generated either by high-throughput screening (HTS) either by selective optimization of side activity, the SOSA approach. In other studies the "hopping" in a different molecular scaffold has relied upon the intuition and/or the experience of the medicinal chemist working on the project.

Most of the virtual screening studies aiming to hop in iso-functional molecules are based on the bioisosterism concept that structural likeness predicts analogous biological activity. At a first glance it can be concluded that a rational approach to scaffold hopping is not possible. Indeed molecular modeling and chemoinformatics experts have set up a lot of softwares and methods to address the paradox of scaffold hopping and bioisosterism and find a logical process.

Among the virtual screening techniques reported so far four types of computational approaches for the scaffold hopping can be distinguished: (a) shape matching, (b) pharmacophore searching, (c) fragment replacement, and (d) similarity searching.

Most of the programs offer combinations of several approaches and they are used, according to the case scenario of a given project, either as on a ligand-based virtual screening base either on a structure (receptor)-based screening.

# FUNCTIONAL GROUP MODIFICATION. Scaffold Hopping

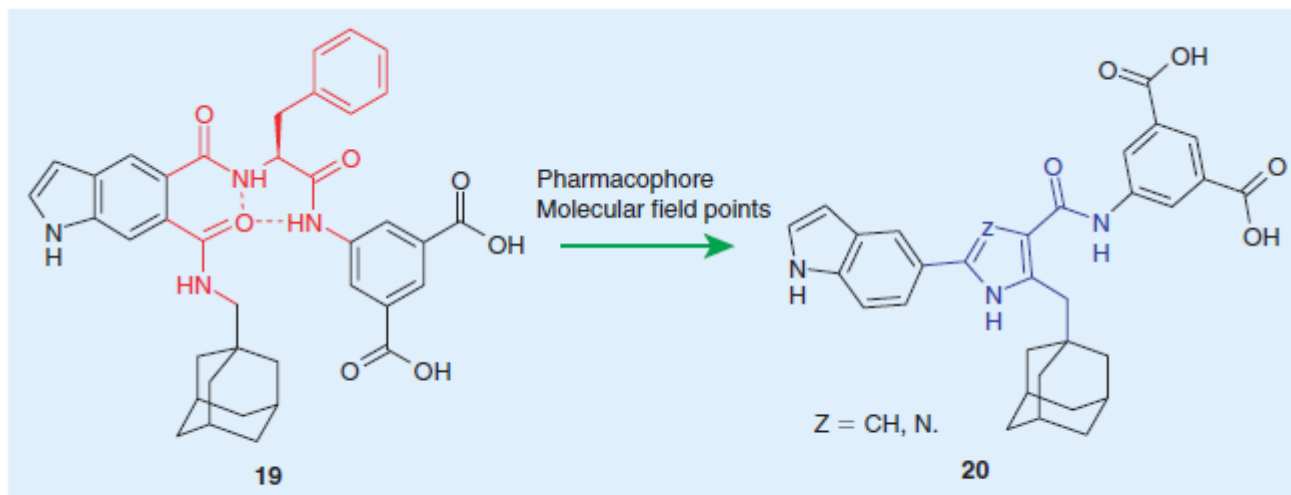


FIGURE 15.56 Design of a novel CCK<sub>2</sub> antagonist via a scaffold hopping approach from a known series of indoles.

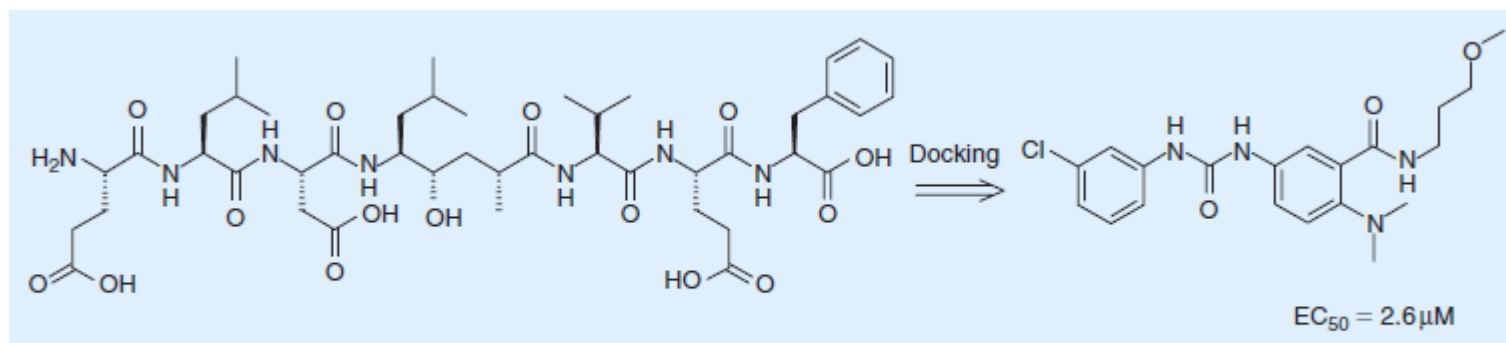


FIGURE 15.57 Discovery of non-peptide inhibitor of  $\beta$ -secretase by high-throughput docking.