Medicinal Chemistry

Drug design: optimizing target interactions

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2021-2022

Drug design: optimizing target interactions

Introduction

Once it ***has* been discovered** ,the **lead compound** can be used as the **starting point** **for** **drug design**.

There are **various aims** in drug design.

The eventual drug should have

1. **- selectivity** and
2. - **good level of activity for its target**, and
3. - **minimal side effects**.
4. - It should be **easily synthesized** and
5. - be **chemically stable**.
6. - Finally, it should **have acceptable pharmacokinetic** properties and **be nontoxic.**

Drug design: optimizing target interactions

- In this chapter, **we concentrate** on **the design strategies** that can be used **to optimize the interaction** **of the drug** **with its target,** in other words its **pharmacodynamic properties**.

- **The design strategies** that **can improve the drug's ability to reach its target** and to **have an acceptable lifetime** are the drug's **pharmacokinetic properties**.

- **Pharmacodynamics** and **pharmacokinetics** should have **equal priority** in influencing ***which strategies*** are **used** and ***which analogues*** **are** **synthesized**.

Drug design: optimizing target interactions

1 Structure-activity relationships

Once the structure of a lead compound is known, the medicinal chemist moves on to study its structure-activity relationships (SAR).

1) **The aim here is to discover :**
   - **which parts of the molecule are important to biological activity and**
   - **which are not.**
2) **If it is possible to crystallize the target with the drug bound to the binding site, the crystal structure of the complex could be solved by X-ray crystallography, then studied with molecular modelling software to identify important binding interactions.**

   If that is the case, it will be necessary

   - **to revert to the traditional method of synthesizing a selected number of compounds that vary slightly from the original structure, then**
   - **studying what effect that has on the biological activity.**

1 Structure-activity relationships

3) Let us imagine that we have isolated a natural product with the structure shown in Fig. 10.2. We shall name it glipine.

4) There are a variety of functional groups present in the structure and the diagram مِبْيان shows the potential binding interactions that are possible with a target binding site.

5) It is unlikely that all of these interactions take place, so we have to identify those that do.

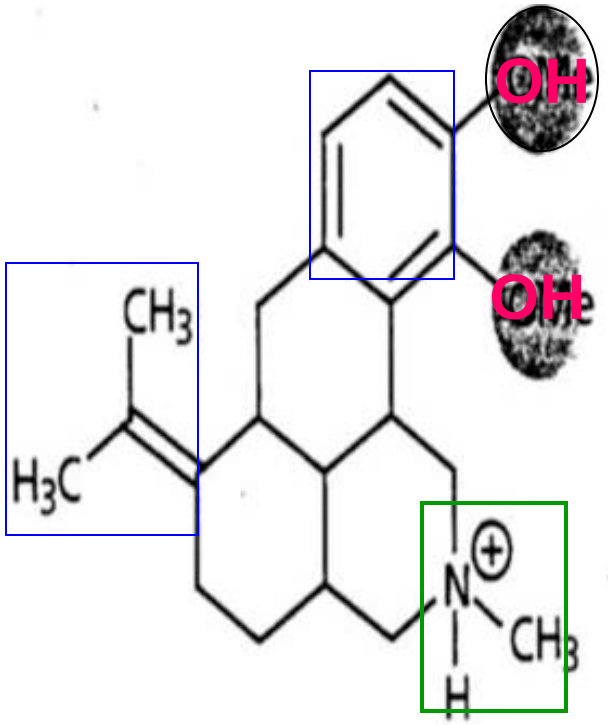

Figure 10.2 Glipine

- Ionic binding group
- Van der Waals binding groups
- H-bond binding groups

Drug design: optimizing target interactions

1 Structure-activity relationships

6) By synthesizing compounds (such as the examples shown in Fig. 10.3) where *one particular functional group of the molecule is removed or altered*, it is possible to find out which groups are essential and which are not.

7) This involves: *testing all the analogues* for biological activity and comparing them with the original compound. If an analogue shows a significantly lowered activity, then the group that has been modified must have been important. If the activity remains similar, then the group is not essential.

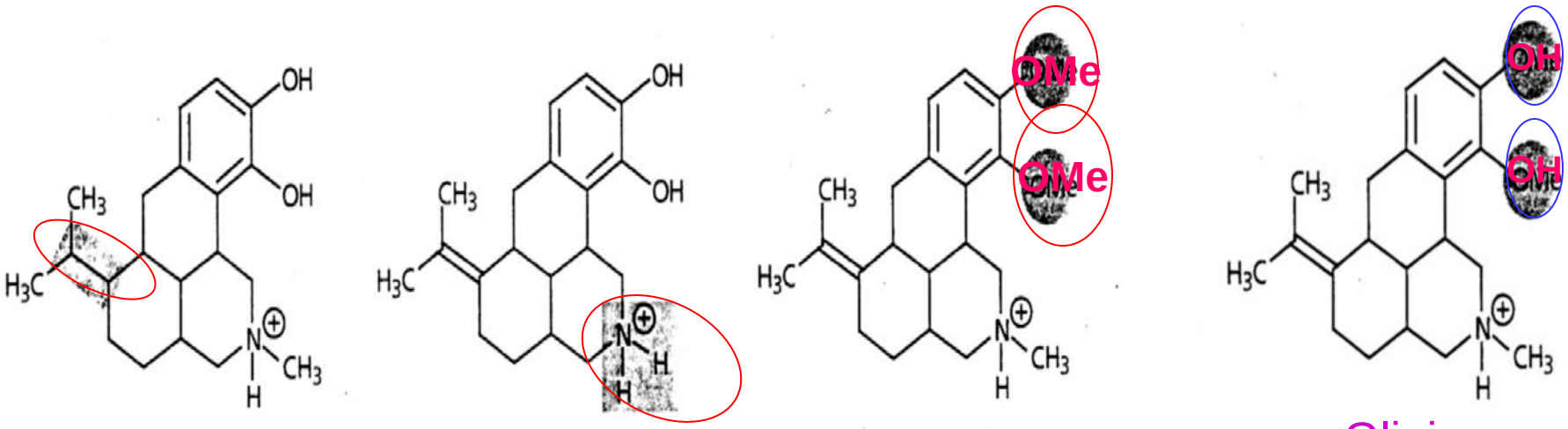

Figure 10.3 Modifications of glipine.

Glipine

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1 Structure-activity relationships

1.1 Binding role of alcohols and phenols

1) The oxygen can act as a hydrogen bond acceptor, and the hydrogen can act as a hydrogen bond donor (Fig. 10.4).

2) One or all of these interactions may be important in binding the drug to the binding site

3) Synthesizing a methyl ether or an ester analogue would be relevant in testing this, as it is highly likely that the bonding would be disrupted in either analogue.

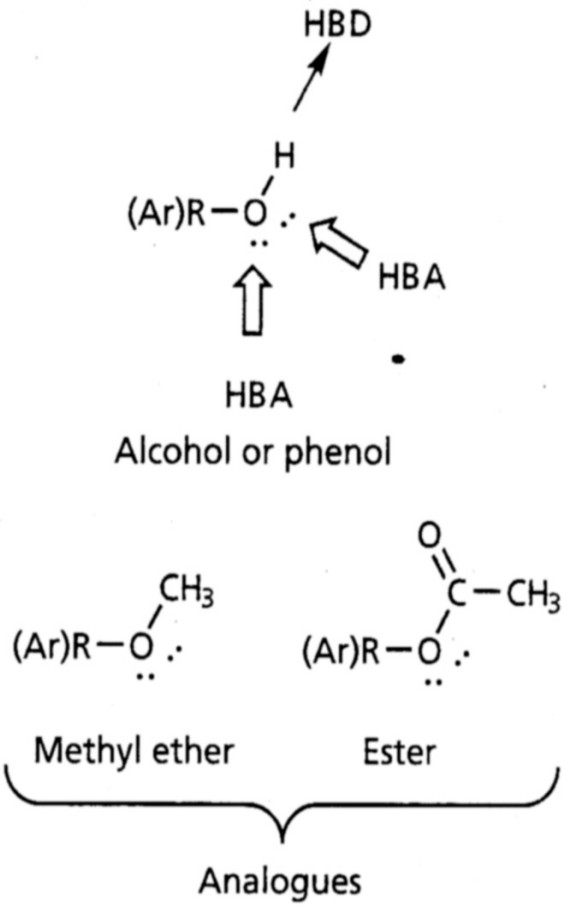


Figure 10.4 Possible hydrogen bonding interactions for an alcohol or phenol.

Drug design: optimizing target interactions

1 Structure-activity relationships

1.1 Binding role of alcohols and phenols

4) Let us consider the methyl ether first.

There are two reasons why the ether might hinder or prevent the hydrogen bonding of the original alcohol or phenol:

1 - The proton of the original hydroxyl group is lost (Frames 1 and 2 in Fig. 10.5).

2 - However, suppose the oxygen atom is acting as a hydrogen bond acceptor (Frame 3 in Fig. 10.5):

The oxygen is still present in the ether analogue, so could it still take part in hydrogen bonding? Well, it may, but possibly not to the same extent (be weakened).

The extra bulk of the methyl group should hinder the close approach that was previously attainable and should disrupt hydrogen bonding (Frame 4 in Fig. 10.5).

Drug design: optimizing target interactions

1 Structure-activity relationships

1.1 Binding role of alcohols and phenols

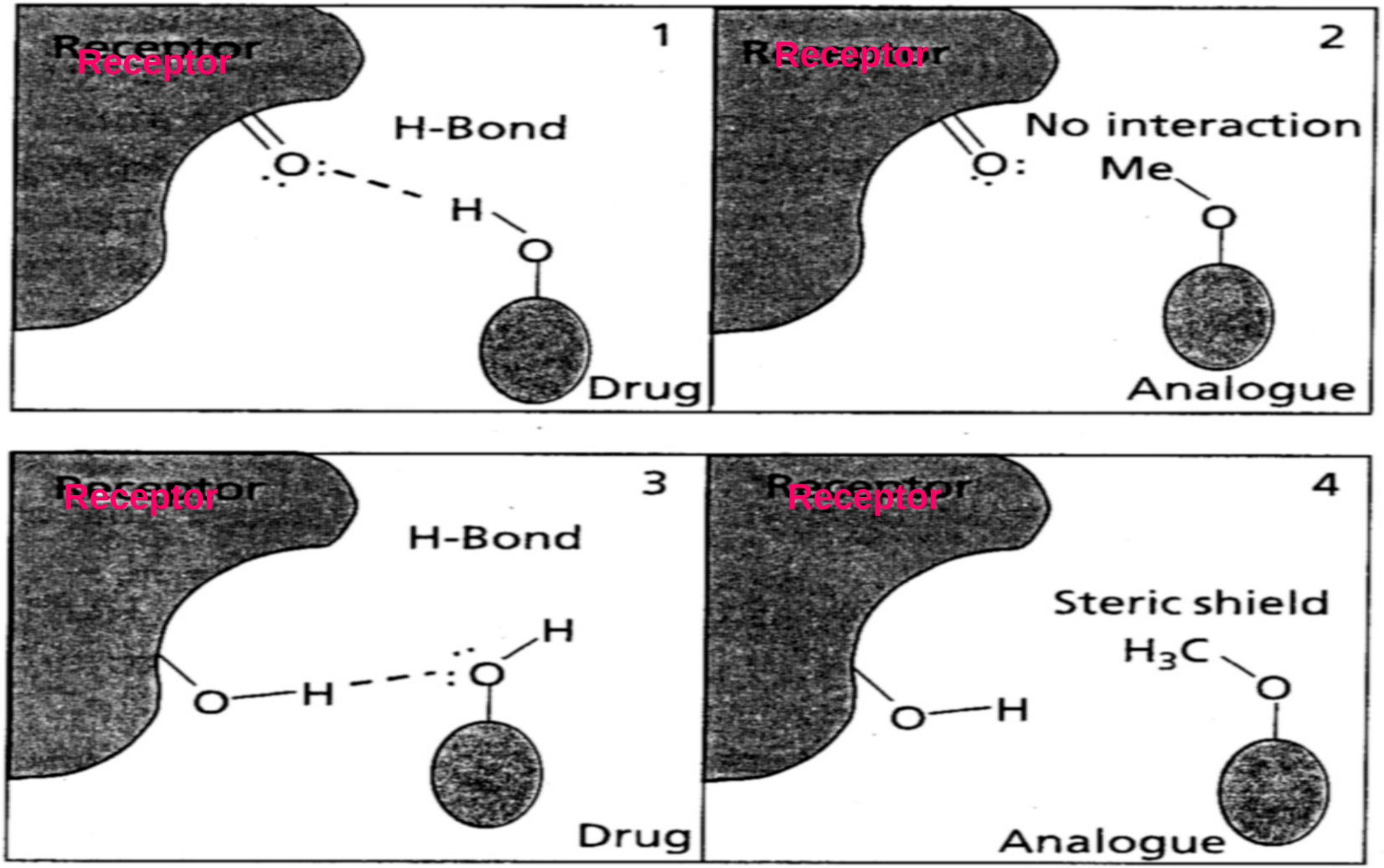


Figure 10.5 Possible hydrogen bond interactions.

Drug design: optimizing target interactions

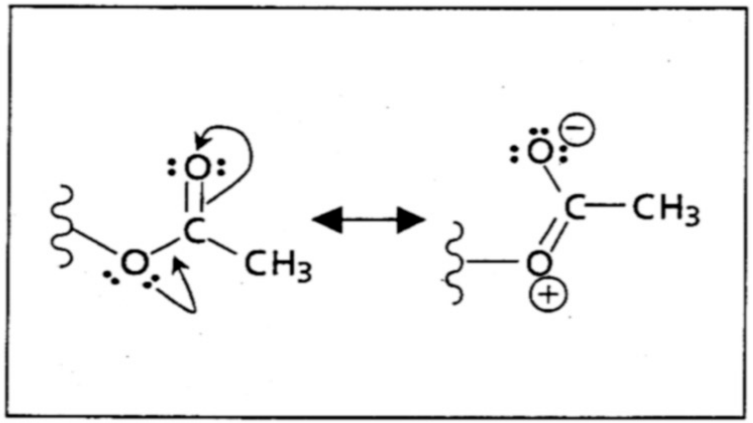
1 Structure-activity relationships

1.1 Binding role of alcohols and phenols

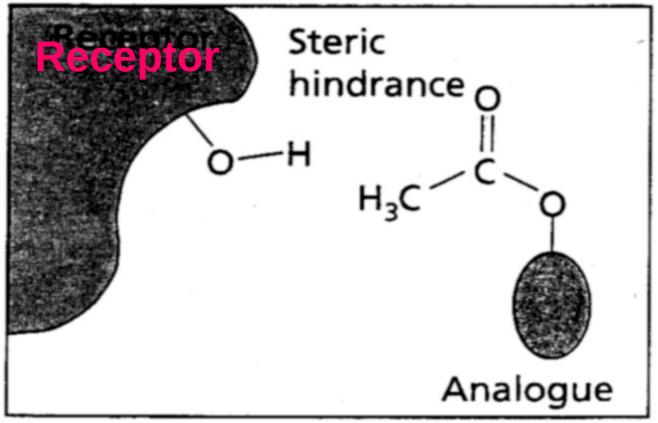
5) The ester analogue:

- **cannot act as a hydrogen bond donor either.**

- **There is still the possibility of it acting as a hydrogen bond acceptor, but the extra bulk of the acyl group is even greater than the methyl group of the ether, and this too should hinder the original hydrogen bonding interaction.**



Electronic factor



Steric factor

Figure 10.6 Factors by which an ester group can disrupt hydrogen bonding of the original hydroxyl group.

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1 Structure-activity relationships

1.2 Binding role of aromatic rings

1- Aromatic rings are planar, hydrophobic structures, commonly involved in van der Waals and hydrophobic interactions with flat hydrophobic regions of the binding site.

2- An analogue containing a cyclohexane ring in place of the aromatic ring is less likely to bind so well, as the ring is no longer flat :

The **axial protons can interact weakly, but they also serve as buffers to keep the rest of the cyclohexane ring at a distance (Fig. 10.7).**

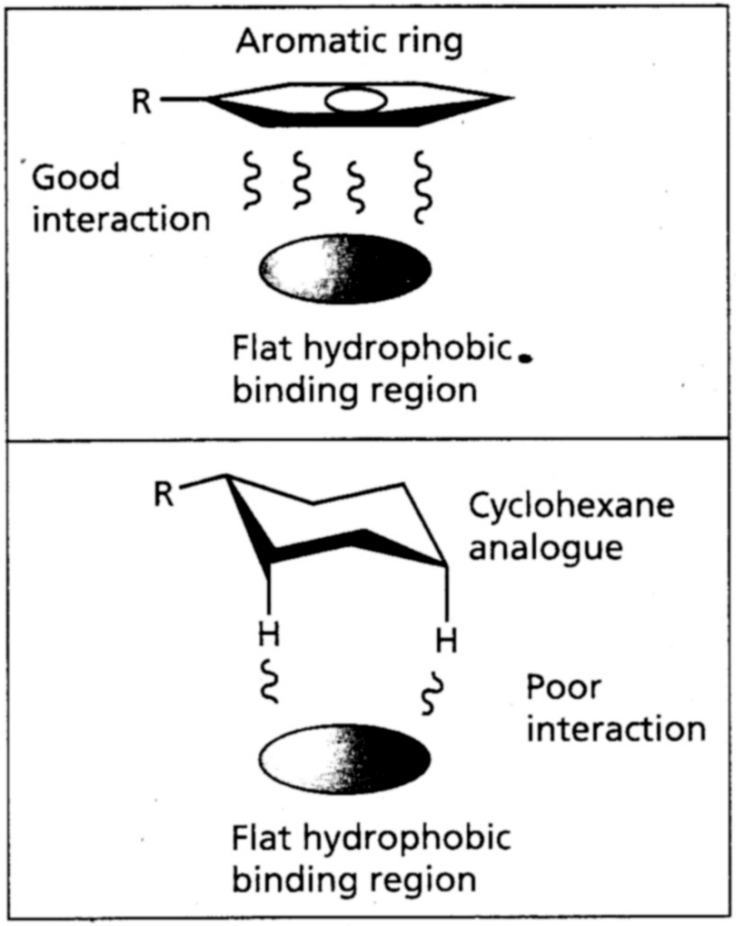

Figure 10.7 Binding comparison of an aromatic ring with a cyclohexyl ring.

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1 Structure-activity relationships

1.3 Binding role of alkenes

1- **Like aromatic rings**, **alkenes** **are planar** and **hydrophobic** so they too can interact with **hydrophobic regions** **of the binding site** through **van der Waals** **and hydrophobic interactions.**

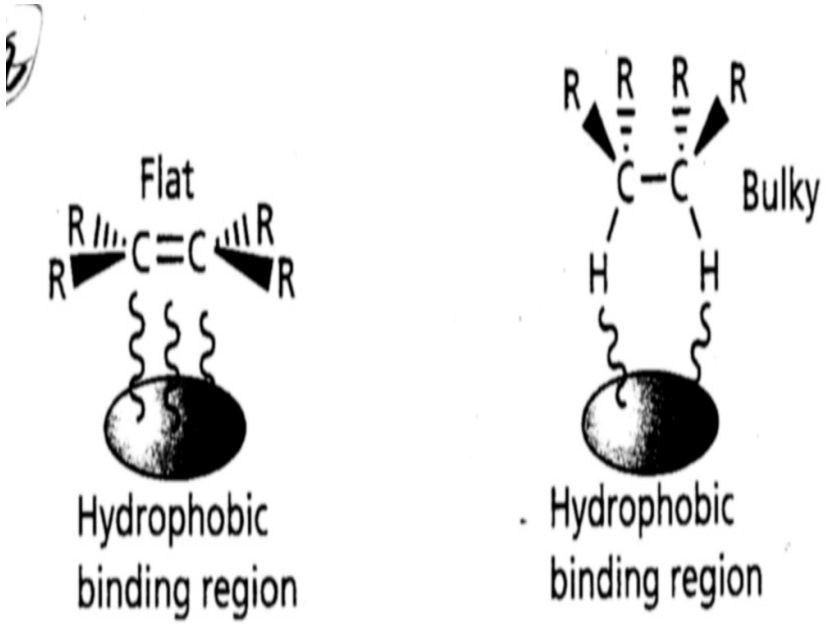


Fig. 10.8. Binding comparison of an alkene with an alkane.

2- The activity of the equivalent saturated analogue would be worth testing, since the saturated alkyl region is bulkier and cannot approach the relevant region of the binding site so closely (Fig. 10.8).

Drug design: optimizing target interactions

1 Structure-activity relationships

1.4 Binding role of ketones and aldehydes

1- A ketone {and an aldehyd(less common)},

It is a planar group that can interact with a binding site through hydrogen bonding where the carbonyl oxygen acts as a hydrogen bond acceptor (Fig. 10.9).

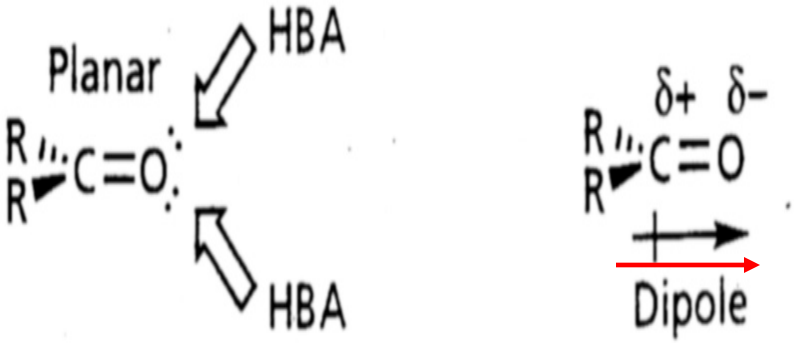


Figure 10.9 Binding interactions that are possible for a carbonyl group.

The lone pairs are in sp^2 hybridized orbitals, which are in the same plane as the functional group.

The carbonyl group also has a significant dipole moment and so a dipole-dipole interaction with the binding site is also possible

Drug design: optimizing target interactions

1 Structure-activity relationships

1.4 Binding role of ketones and aldehydes

2- It is relatively easy to reduce a ketone to an alcohol and it may be possible to carry out this reaction directly on the lead compound.

This significantly changes the geometry of the functional group, from planar to tetrahedral.

Such an alteration in geometry may well :

weaken **any existing hydrogen bonding interactions and will certainly**

weaken **any dipole-dipole interactions, as both the magnitude and orientation of the dipole moment will be altered (Fig. 10.10).**

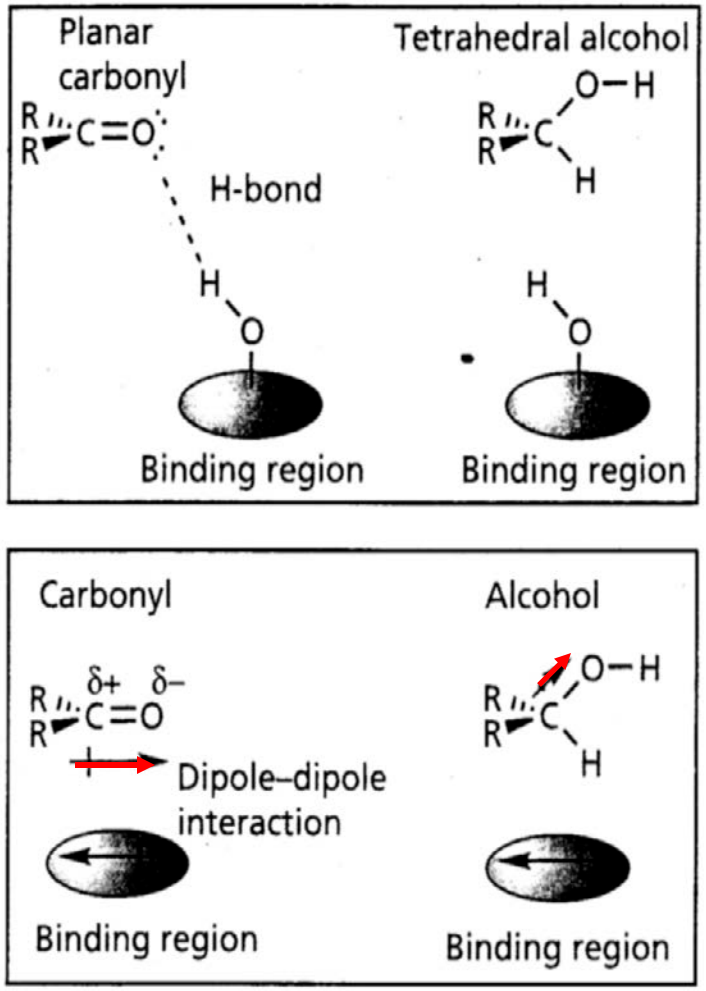


Figure 10.10 Effect on binding interactions following the reduction of a ketone or aldehyde.

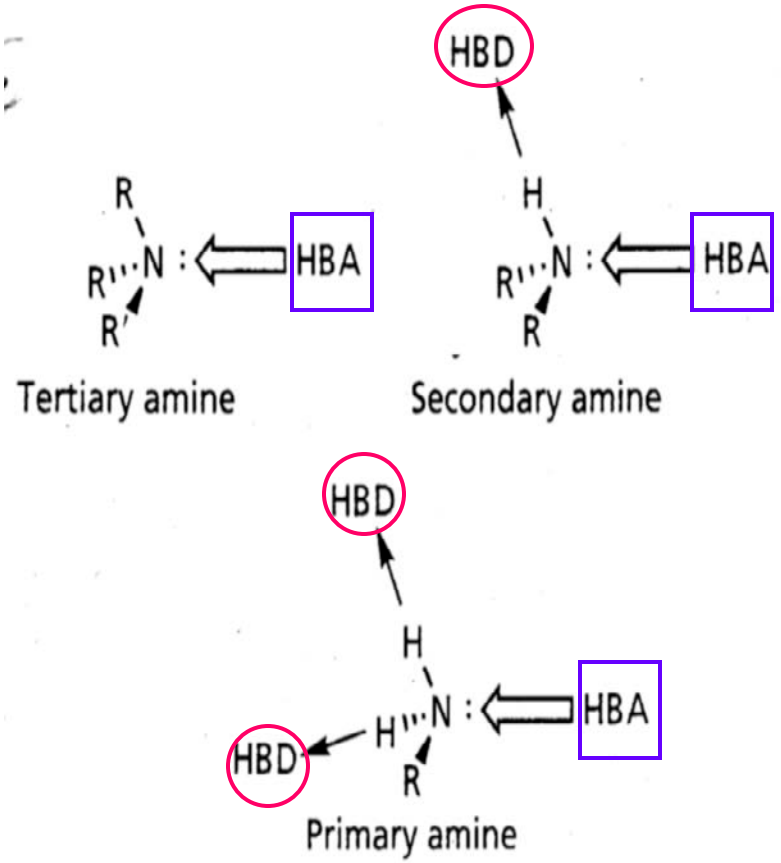
Drug design: optimizing target interactions

1 Structure-activity relationships

1.5 Binding role of amines

They may be involved in hydrogen bonding either as a hydrogen bond acceptor or a hydrogen bond donor (Fig. 10.11).

1. **The nitrogen atom has one lone pair of electrons and can act as a hydrogen bond acceptor for one hydrogen bond.**
2. **Primary and secondary amines have *N*-H groups and can act as hydrogen bond donors.**
3. ***Aromatic and heteroaromatic amines* act only as hydrogen bond donors, because the lone pair interacts with the aromatic or heteroaromatic ring.**



Drug design: optimizing target interactions

1 Structure-activity relationships

1.5 Binding role of amines

4. In many cases, the amine may be protonated when it interacts with its target binding site, which means that it is ionized and cannot act as a hydrogen bond acceptor.

   However, it can still act as a hydrogen bond donor and will form a stronger hydrogen bond than if it was not ionized (Fig. 10.12).

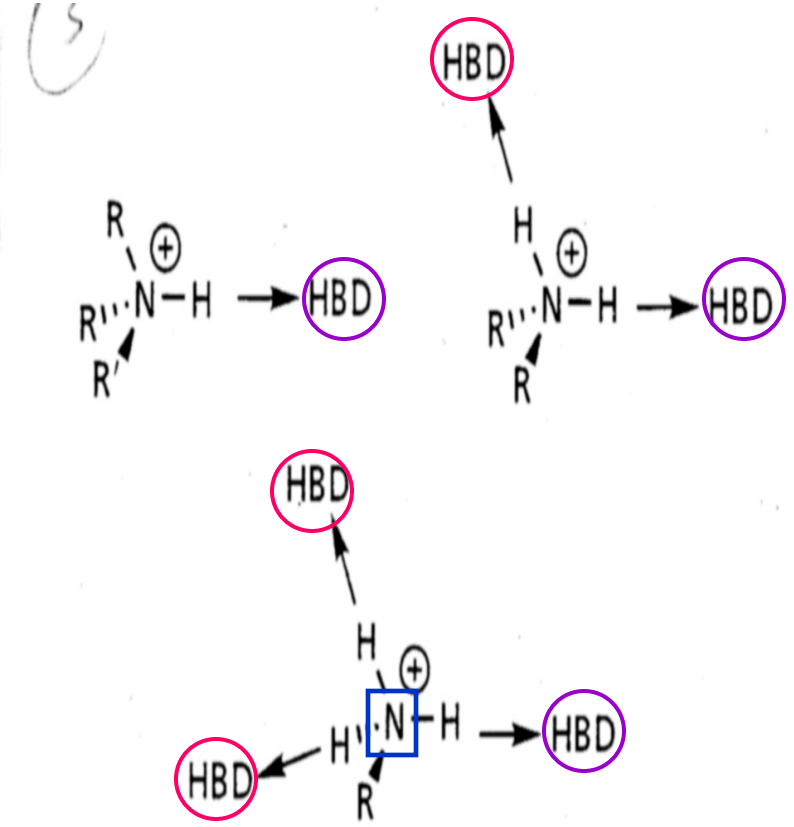


Figure 10.12 Possible hydrogen bonding interactions for ionized amines.

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1 Structure-activity relationships

1.5 Binding role of amines

5. **Alternatively, a strong ionic interaction may take place with a carboxylate ion in the binding site (Fig. 10.13).**

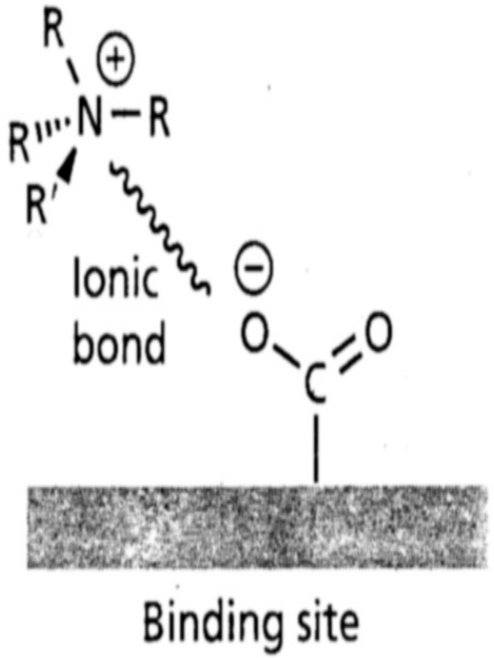


Figure 10.13 Ionic interaction between an ionized amine and a carboxylate ion.

Drug design: optimizing target interactions

1 Structure-activity relationships

1.6 Binding role of amides

Amides are likely to interact with binding sites through hydrogen bonding (Fig. 10.16).

1) **The carbonyl oxygen atom can act as a hydrogen bond acceptor and has the potential to form two hydrogen bonds.**

2) ***The nitrogen cannot act as a hydrogen bond acceptor because the lone pair interacts with the neighbouring carbonyl group, as described above.***

3) **Primary and secondary amides have an *N*-H group, which allows the possibility of this group acting as a hydrogen bond donor.**

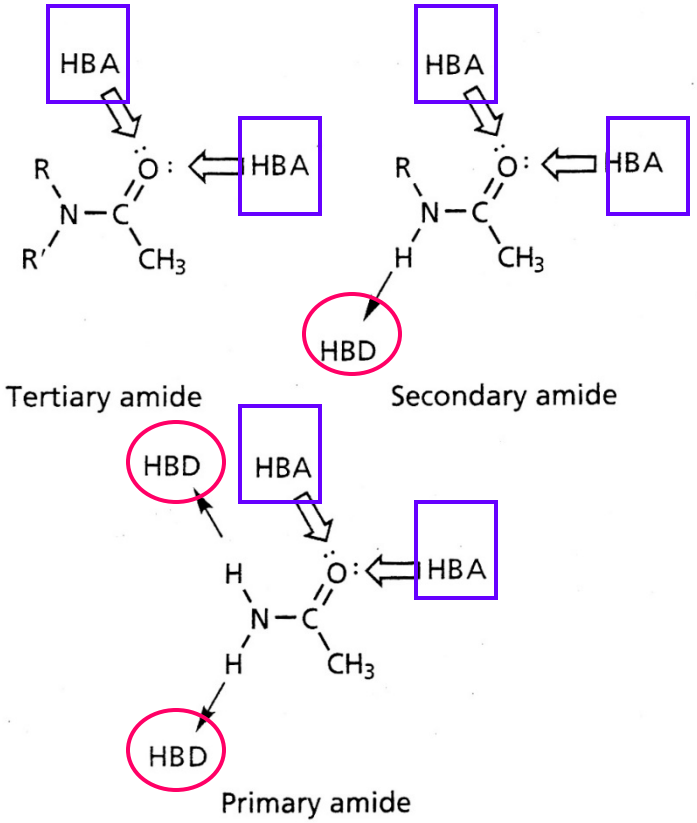


Figure 10.16 Possible hydrogen bonding interactions for amides.

Drug design: optimizing target interactions

1 Structure-activity relationships

1.6 Binding role of amides

4) **Amides which are within a ring system are called lactams.**

5) **If the ring is small and suffers ring strain, lactam can undergo a chemical reaction with the target leading to the formation of a covalent bond.**

The best examples of this are the penicillins, which contain a four-membered R-lactam ring. This acts as an acylating agent and irreversibly inhibits a bacterial enzyme by acylating a serine residue in the active site (Fig. 10.18)

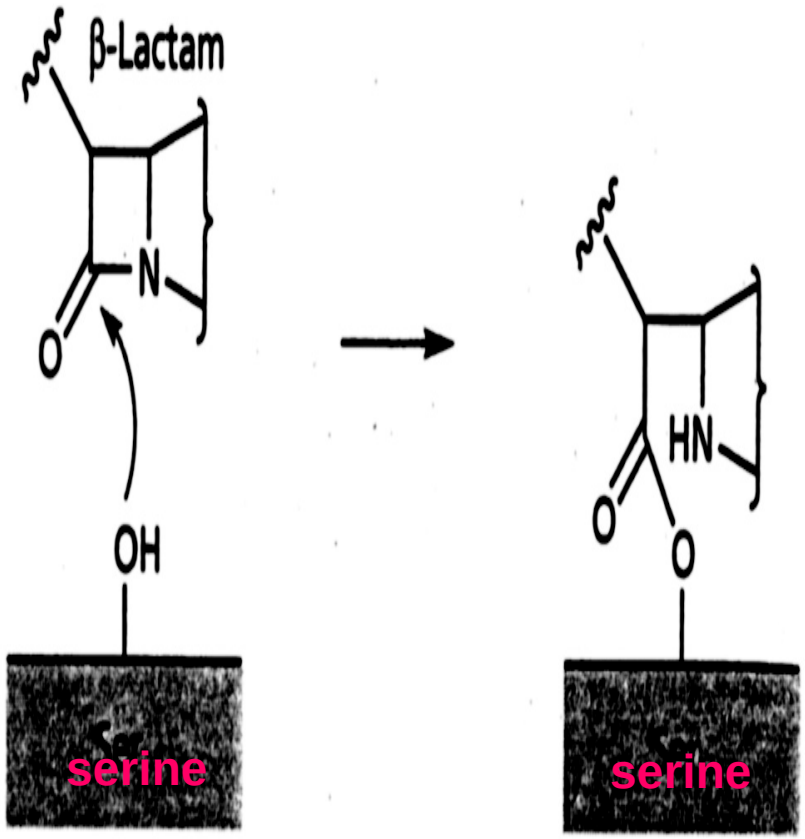


Figure 10.18 β-lactam ring acting as an acylating agent.

Drug design: optimizing target interactions

1 Structure-activity relationships

1.7 Binding role of quaternary ammonium salts

1- Quaternary ammonium salts are **ionized and can interact with carboxylate groups by ionic interactions (Fig. 10.19).**

2- Another possibility is an induced dipole interaction between the quaternary ammonium ion and any aromatic rings in the binding site.

The positively charged nitrogen can distort يحرف the π electrons of the aromatic ring such that a dipole is induced, whereby the face of the ring is slightly negative and the edges are slightly positive.

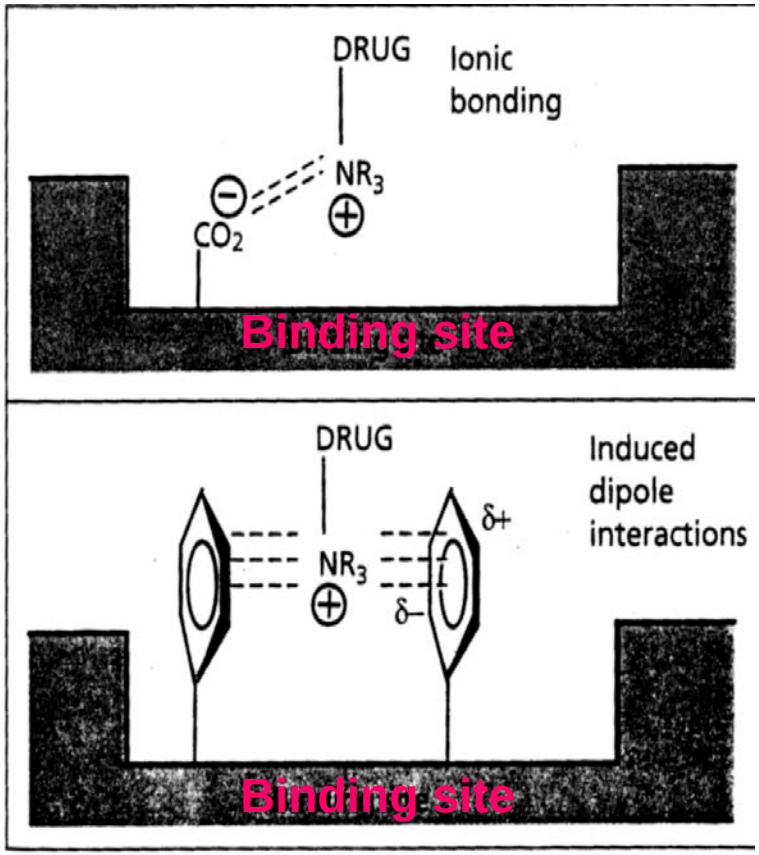


Figure 10.19 Possible binding interactions of a quaternary ammonium ion.

Drug design: optimizing target interactions

1 Structure-activity relationships

1.8 Binding role of carboxylic acids

1-The carboxylic acid group is reasonably common in drugs. It can act as a hydrogen bond acceptor in various ways, or as a hydrogen bond donor (Fig. 10.20).

2- Alternatively, it may exist as the carboxylate ion. This allows the possibility of:

- an ionic interaction or
- a strong hydrogen bond where the carboxylate ion acts as the hydrogen bond acceptor.

3-The carboxylate ion has also been found to be *a good ligand for zinc ions*, which are present as cofactors in enzymes known as zinc metalloproteinases.

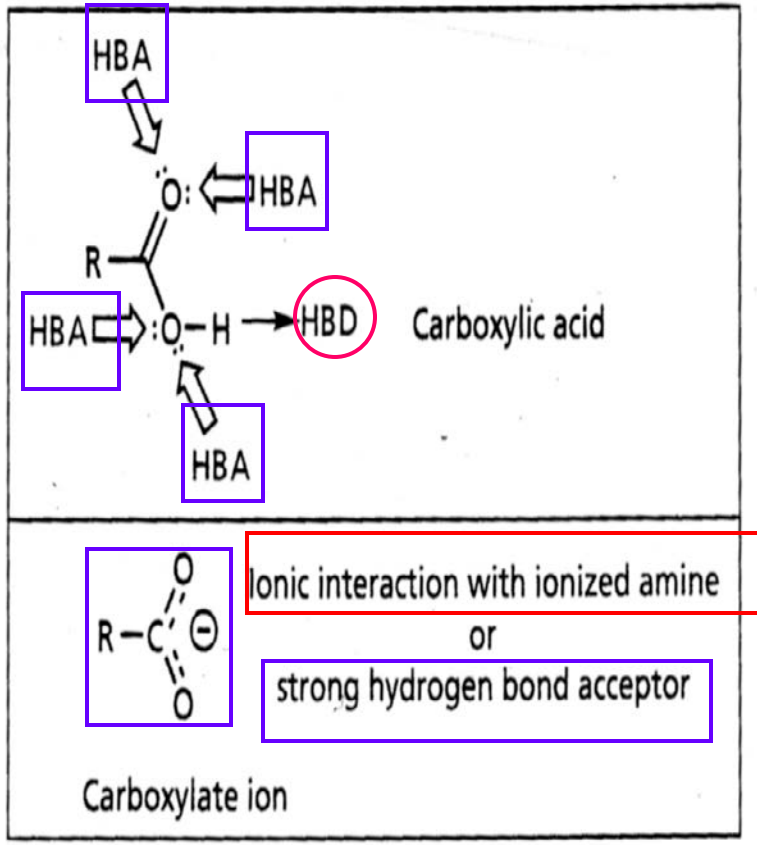


Figure 10.20 Possible binding interactions for a carboxylic acid and carboxylate ion.

Drug design: optimizing target interactions

1 Structure-activity relationships

1.8 Binding role of carboxylic acids

4- In order to test the possibility of such interactions, analogues such as esters, primary alcohols, and ketones could be synthesized and tested (Fig. 10.21). *None of these functional groups can ionize, so a loss of activity could imply that an ionic bond is important.*

5-The primary alcohol could shed light on whether the carbonyl oxygen is involved in hydrogen bonding, whereas the ester and ketone could indicate whether the hydroxyl group of the carboxylic acid is involved in hydrogen bonding.

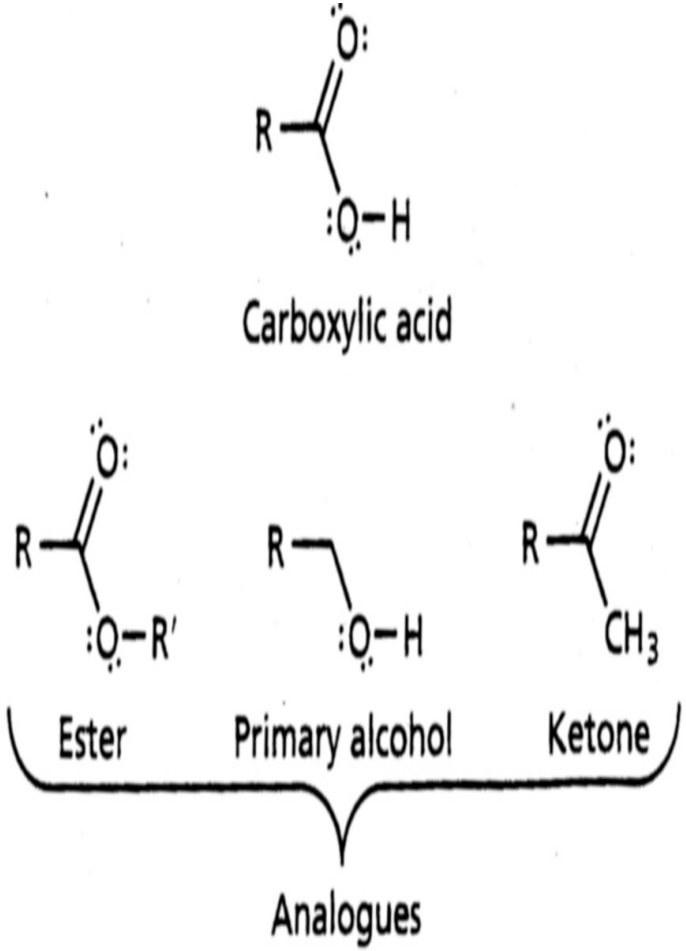


Figure 10.21 Analogues for a carboxylic acid.

Drug design: optimizing target interactions

1 Structure-activity relationships

1.9 Binding role of esters

1. An ester functional group has the potential to interact with a binding site as a hydrogen bond acceptor only (Fig. 10.22).
2. The carbonyl oxygen is *more* likely to act as the hydrogen bond acceptor than the alkoxy oxygen, as it is :1) *sterically less hindered* and 2)*has a greater electron density*.
3. The importance or otherwise of the carbonyl group could be judged by testing an equivalent ether, which would require a full synthesis.

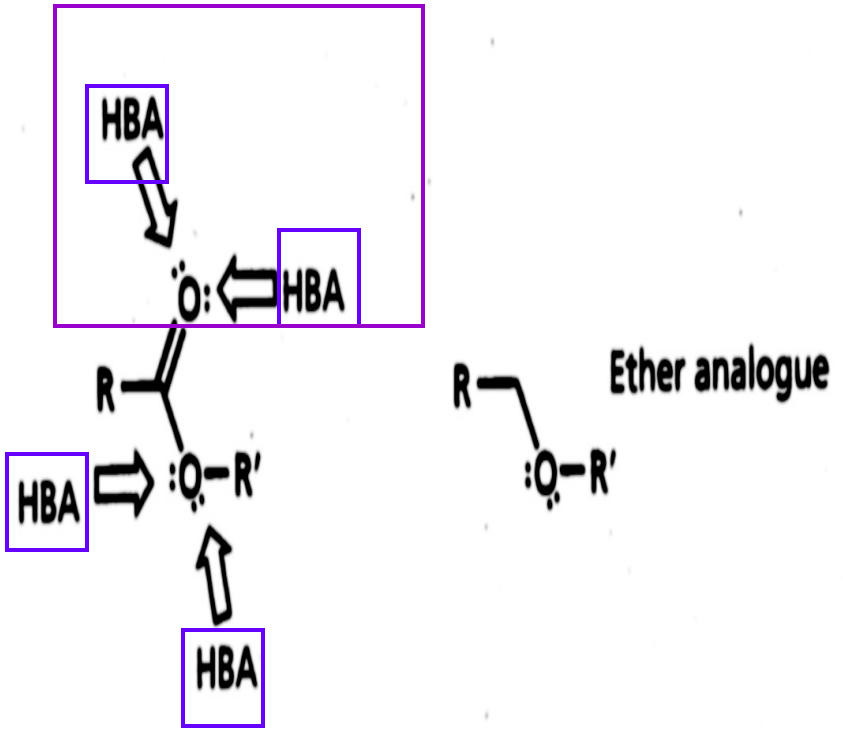


Figure 10.22 Possible binding interactions for an ester.

Drug design: optimizing target interactions

1 Structure-activity relationships

1.9 Binding role of esters

4. **Esters are susceptible to hydrolysis *in vivo* by metabolic enzymes called esterase.**

   This may pose a problem if the lead compound contains an ester that is important to binding, as it means the drug might have a short lifetime *in vivo*.

5. **Having said that, there are several drugs that *do* contain esters and are relatively stable to metabolism, thanks to either:**

   1) electronic factors that stabilize the ester or

   2) steric factors that protect it.

1.9 Binding role of esters

6. Esters that are susceptible to metabolic hydrolysis are sometimes used deliberately to mask a polar functional group such as a carboxylic acid, alcohol or phenol in order to achieve better absorption from the gastrointestinal tract.

7. Once in the blood supply, the ester is hydrolysed to release the active drug. This is known as a prodrug strategy.

why Medicinal chemist sometimes used deliberately Esters in designing a drug despite they are susceptible to metabolic hydrolysis

Drug design: optimizing target interactions

1 Structure-activity relationships

1.9 Binding role of esters

8. **Special mention should be made of the ester group in aspirin.**

Aspirin has an anti-inflammatory action resulting from its ability to inhibit an enzyme called cyclooxygenase (COX):

In this case the ester is not taking part in intermolecular bonding but acts as an acylating agent where an acetyl group is covalently attached to a serine residue in the active site (Fig. 10.23).

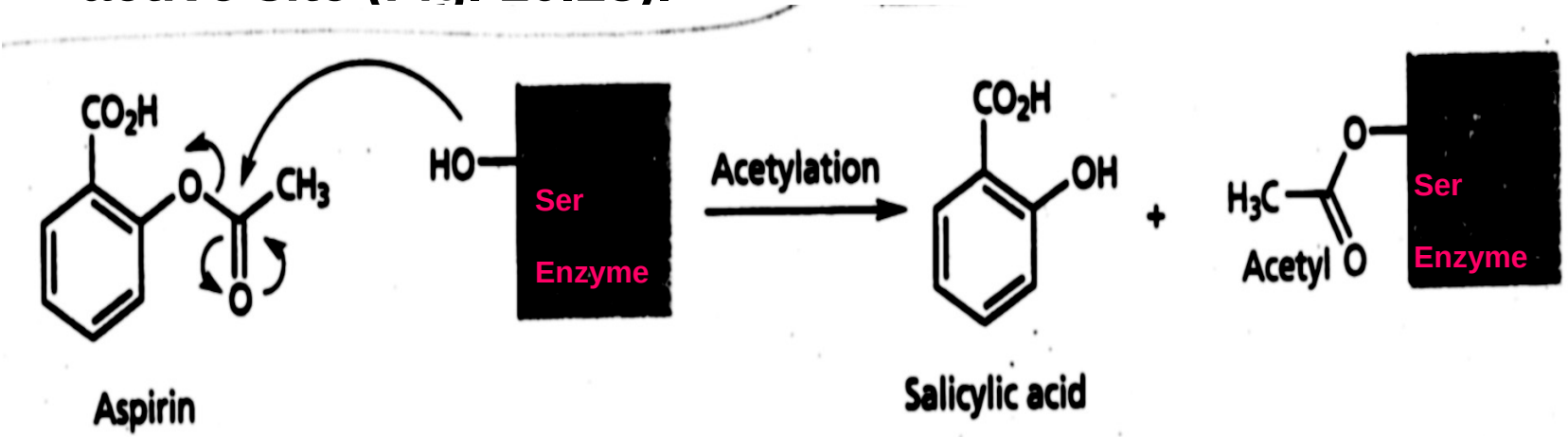


Figure 10.23 Aspirin acting as an acylating agent.

Drug design: optimizing target interactions

1 Structure-activity relationships

1.10 Binding role of alkyl and aryl halides

1. **Alkyl halides involving chlorine, bromine, or iodine tend to be chemically reactive, since the halide ion is a good leaving group.**

   As a result, a drug containing an alkyl halide is likely to react with any nucleophilic group and become permanently linked to that group by a covalent bond --an alkylation reaction (Fig. 10.24).

1) **- This poses a problem, as the drug is likely to alkylate a large variety of macromolecules which have nucleophilic groups, especially proteins and nucleic acids.**

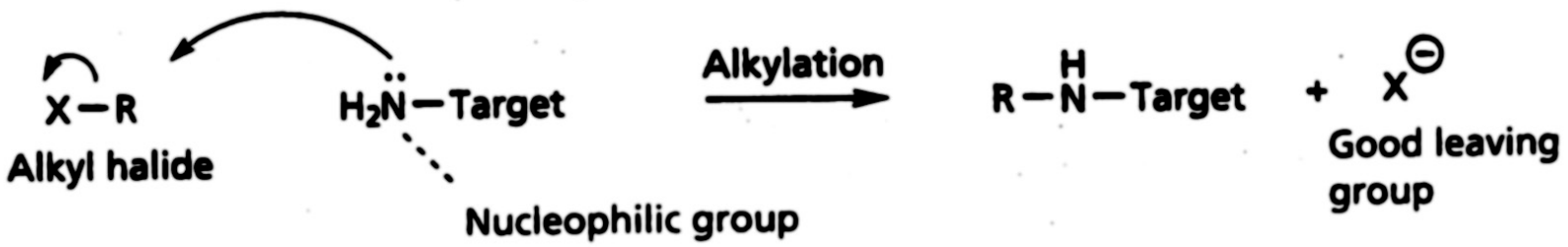


Figure 10.24 Alkylation of macromolecular targets by alkyl halides.

2) - It is possible to moderate the reactivity to some extent, but selectivity is still a problem and leads to severe side effects.

3) -These drugs are therefore reserved for life-threatening diseases such as cancer.

2. Alkyl fluorides, on the other hand, are not alkylating agents, because the C-F bond is a strong one and is not easily broken.

Fluorine is commonly used to replace a proton as it is approximately the same size, but has different electronic properties. It may also protect the molecule from metabolism.

3. **Aryl halides do not act as alkylating agents** and pose **less of a problem in that respect.**

   As the halogen substituents are electron-withdrawing groups, they affect the electron density of the aromatic ring and this may have an influence on the binding of the aromatic ring.

4. **Aliphatic and aromatic analogues lacking the halogen substituent could be prepared by a full synthesis to test whether the halogen has any importance in the activity of the lead compound.**

Drug design: optimizing target interactions

1 Structure-activity relationships

1.11 Binding role of thiols

1) **The thiol group (-S-H) is known to be a good ligand for a zinc ion and has been incorporated into several drugs designed to inhibit enzymes containing a zinc cofactor.**

2) **Such enzymes are known as zinc metalloproteinases.**

3) **If the lead compound has a thiol group, the corresponding alcohol could be tested. This would have a far weaker interaction with a transition metal such as zinc.**

Why medicinal chemists incorporate the thiol group (-S-H) into several drugs ?

Drug design: optimizing target interactions

1 Structure-activity relationships

1.12 Binding role of other functional groups

A wide variety of other functional groups may be present in lead compounds that have no direct binding role, but could be important in other respects.

- **Some may influence the electronic properties of the molecule (e.g. nitro groups or nitriles).**
- **Others may restrict the shape or conformation of a molecule (e.g. alkynes) .**
- **Functional groups may also act as metabolic blockers (e.g. alkynes, aryl halides).**

Indicate the importance of some groups incorporated in a new drug despite they don't have a direct binding role?

Why do incorporate a nitro group in the structure of a new drug?

Drug design: optimizing target interactions

1 Structure-activity relationships

1.13 Binding role of alkyl groups and the carbon skeleton

1. The alkyl substituents and carbon skeleton of a lead compound are hydrophobic and may bind with hydrophobic regions of the binding site through van der Waals and hydrophobic interactions.

2. The relevance of an alkyl substituent to binding can be determined by synthesizing an analogue which lacks the substituent.

3. However, if the alkyl group is attached to nitrogen or oxygen, it may be possible to remove the group from the lead compound as shown in Fig. 10.25.

   The analogues obtained may then be expected to have less activity if the alkyl group was involved in important hydrophobic interactions.

Drug design: optimizing target interactions

1 Structure-activity relationships

1.13 Binding role of alkyl groups and the carbon skeleton

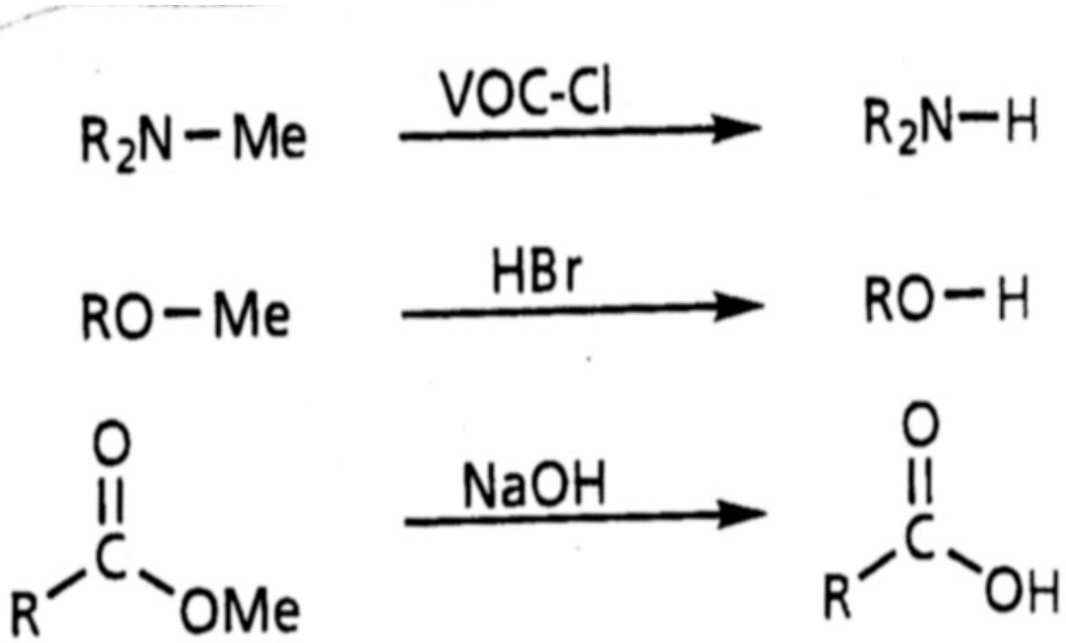


Figure 10.25 Removal of alkyl groups from heteroatoms.

VOC-Cl : Vinyloxycarbonyl chloride

Drug design: optimizing target interactions

1 Structure-activity relationships

1.14 Binding role of heterocycles

1) **Heterocycles are cyclic structures that contain one or more heteroatoms such as oxygen, nitrogen, or sulfur**

2) **Nitrogen-containing heterorycles are particularly prevalent.**

The heterocycles can be aliphatic or aromatic in character, and have the potential to interact with binding sites through a variety of bonding forces.

For example,

- **the overall heterocycle can interact through van der Waals and hydrophobic interactions,**
- **while the individual hetroatoms present in the structure could interact by hydrogen bonding or ionic bonding**

Drug design: optimizing target interactions

1 Structure-activity relationships

1.14 Binding role of heterocycles

- As far as hydrogen bonding is concerned, there is an important directional توجيهي aspect جانِبٌ:

  a- The position of the heteroatom in the ring and

  b- the orientation of the ring in the binding site can be crucial in determining whether or not a good interaction takes place.

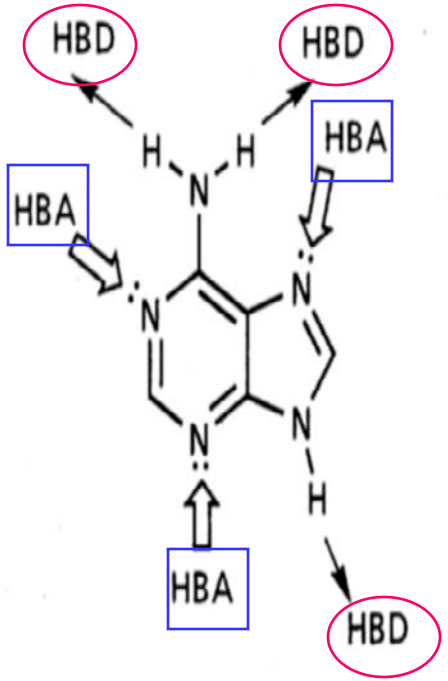


Figure 10.26 Possible hydrogen bonding interactions for adenine.

For example, a purine ring (adenine)can take part in six hydrogen bonding interactions, three as a hydrogen bond donor and three as a hydrogen bond acceptor.

(adenine)

Drug design: optimizing target interactions

1 Structure-activity relationships

1.14 Binding role of heterocycles

If the lead compound contains a heterocyclic ring, it is worth synthesizing analogues containing :

- **an aromatic ring or**
- **different heterocyclic rings**

to explore whether all the heteroatoms present are really necessary.

What are the directional توجيهيaspect جانِبٌ of the heterocyclic ring?

Drug design: optimizing target interactions

1 Structure-activity relationships

1.14 Binding role of heterocycles

3) A complication with heterocycles is the possibility of tautomers. This played an important role in determining the structure of DNA:

A -The structure of DNA consists of a double helix with base pairing between two sets of heterocyclic nucleic acid bases.

B - Base pairing involves three hydrogen bonds between the base pair guanine and cytosine, and two hydrogen bonds between the base pair adenine and thymine (Fig. 10.28).

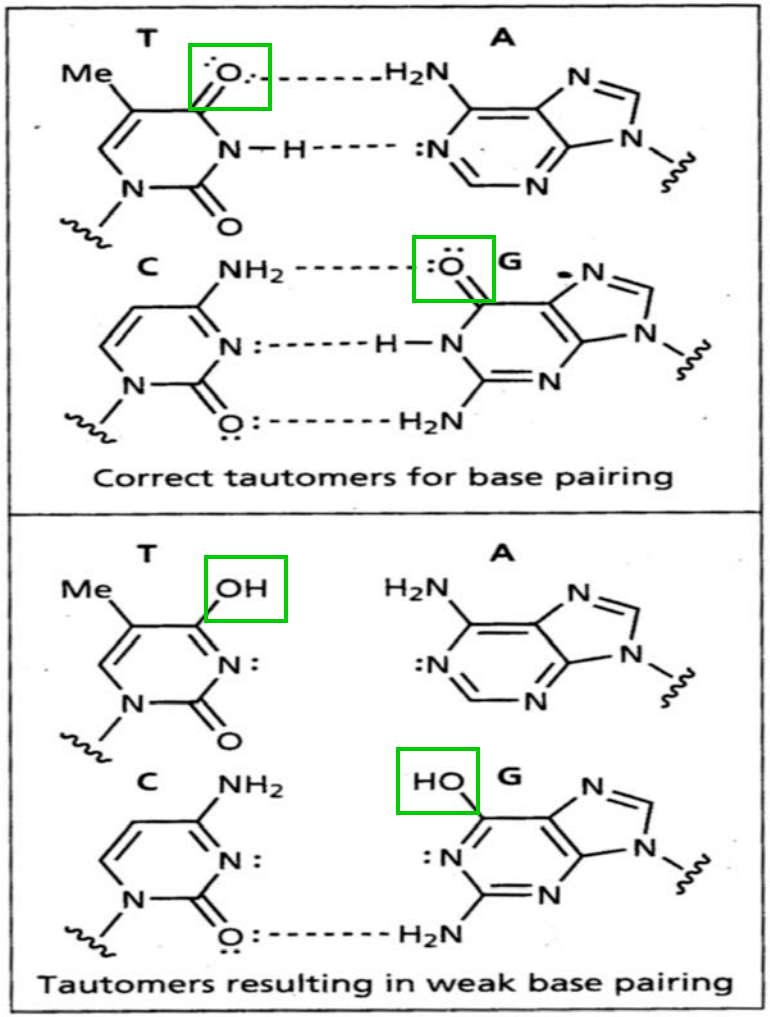


Figure 10.28 Base pairing in DNA and the importance of tautomers.

Drug design: optimizing target interactions`

1 Structure-activity relationships

1.15 Isosteres

1) **Isosteres are atoms or groups of atoms which have 1)- the same valency (or number of outer shell electrons), and 2)- chemical or physical similarities (Fig. 10.30).**

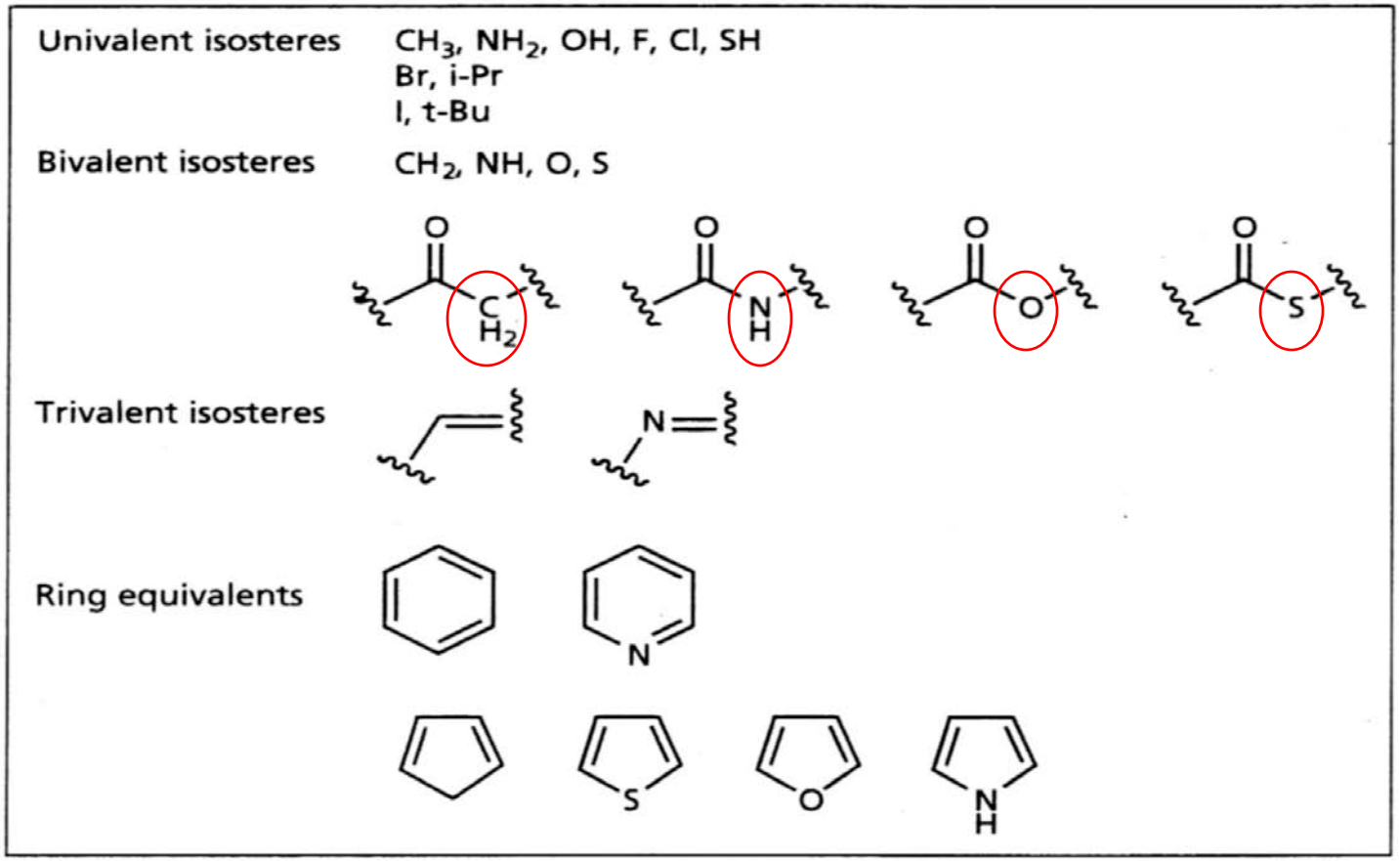


Figure 10.30 Examples of classical isosteres.

Drug design: optimizing target interactions

1 Structure-activity relationships

1.15 Isosteres

2) For example, -SH, $-NH_2$, and $-CH_3$ are isosteres of -OH, whereas S, -NH-, and $-CH_2$ are isosteres of O.

3) Isosteres can be used to determine whether a particular group is an important binding group or not, by altering the character of the molecule in as controlled a way as possible.

- Replacing O with CH_2, for example, will make little difference to the size of the analogue, but will have a marked effect on its 1) polarity, 2) electronic distribution, and 3) bonding.
- Replacing OH with the larger SH may not have such an influence on the electronic character, but steric factors become more significant.

What are the isosteres of –OH?

Wy we use the isost eres ? to determine whether a particular group is an important binding group or not,
to determine whether a particular group is involved in hydrogen bonding.

Drug design: optimizing target interactions

1 Structure-activity relationships

1.15 Isosteres

4) Isosteric groups could be used to determine whether a particular group is involved in hydrogen bonding. For example,

- replacing -OH with $-CH_3$ would completely eliminate hydrogen bonding, whereas
- replacing -OH with $-NH_2$ would not.

5) The (β-blocker propranolol has an ether linkage (Fig. 10.31):

- Replacement of the $-OCH_{2-}$ segment with the isosteres -CH=CH-, $-SCH_{2-}$, or $-CH_2CH_{2-}$ eliminates activity, whereas
- replacement with $-NHCH_{2-}$ retains activity (though reduced).

These results show that the ether oxygen is important to the activity of the drug and suggests that it is involved in hydrogen bonding with the receptor.

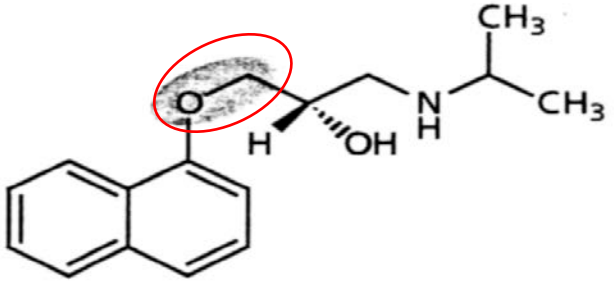


Figure 10.31 Propranolol.

Drug design: optimizing target interactions

2 Identification of a pharmacophore

Once it is established which groups are important for a drug's activity, it is possible to move on to the next stage the identification of the pharmacophore.

The pharmacophore summarizes :

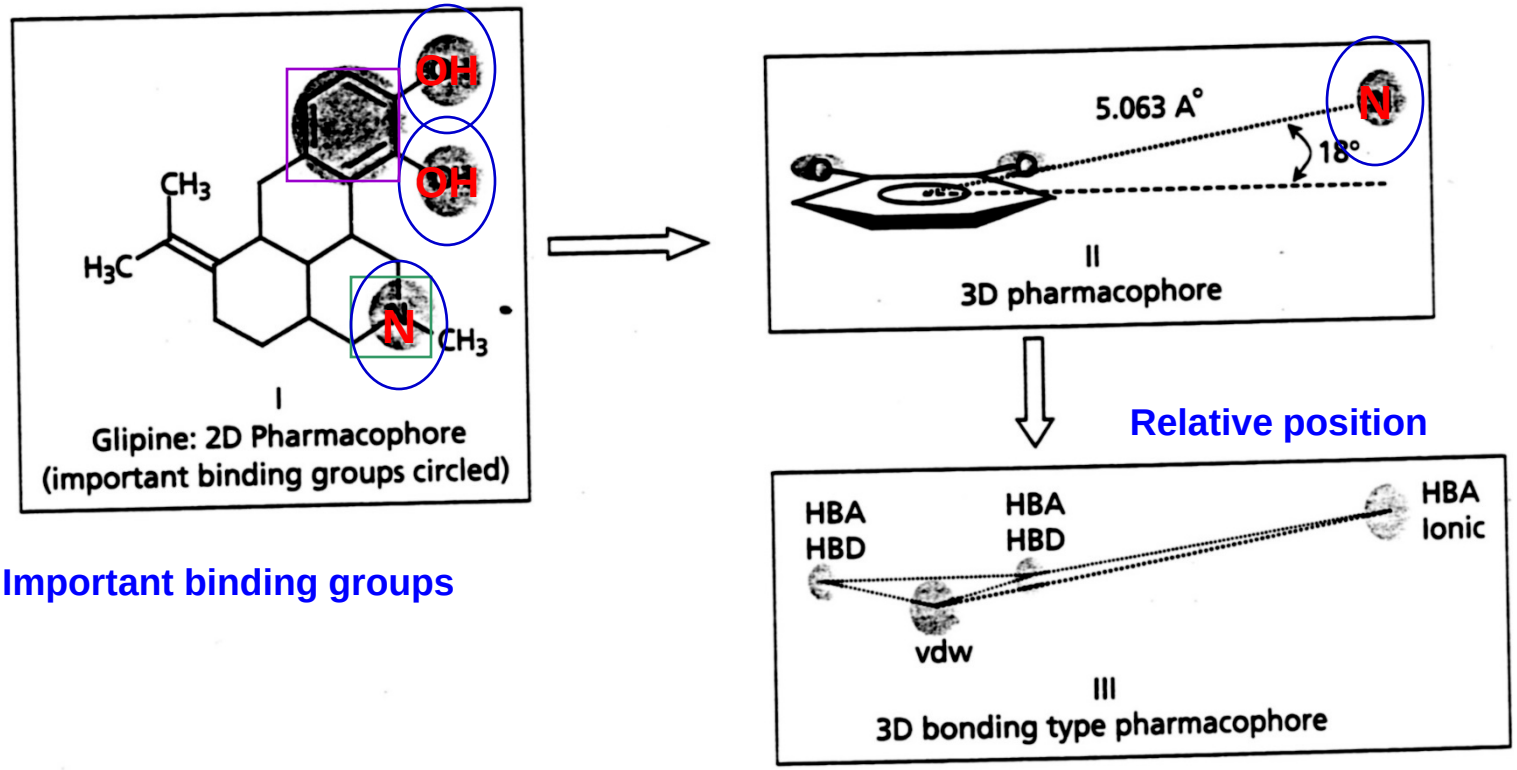
-The important binding groups which are required for activity, and

- their relative positions in space with respect to each other.

For example, if we discover that the important binding groups for our hypothetical drug glipine are the two phenol groups, the aromatic ring, and the nitrogen atom, then the pharmacophore is as shown in Fig.10.32.

Drug design: optimizing target interactions

2 Identification of a pharmacophore



Important binding groups

Figure 10.32 A pharmacophore for glipine.

the **phenol groups** can act as **hydrogen bond donors or acceptors,**

the **aromatic** ring can participate in **van der Waals interactions,** and

the **amine** can act as a **hydrogen bond acceptor or an ionic centre if it is protonated**

3 Drug optimization: strategies in drug design

Once the important binding groups and **pharmacophore of the lead compound have been identified, it is possible to synthesize analogues that contain the same pharmacophore.**

But why is this necessary?

If the lead compound has useful biological activity, why bother making analogues ?

The answer is that:

- **very few lead compounds are ideal.**
- **Most are likely to have 1) low activity,2) poor selectivity, and 3) significant side effects, 4) They may also be difficult to synthesize**

so there is an advantage in finding analogues with improved properties.

We look now at strategies that can be used to optimize the interactions of a drug with its target to allow: higher activity and selectivity.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3.1 Variation of substituents

3.1.1 Alkyl substituents

If alkyl groups are interacting with a hydrophobic pocket in the binding site, then varying the

1) length and

2)bulk

of the alkyl group (e.g. methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or t-butyl) allows one to probe the

1) depth and

2) width of the pocket.

Choosing a substituent that will fill the pocket will then increase the binding interaction (Fig. 10.34).

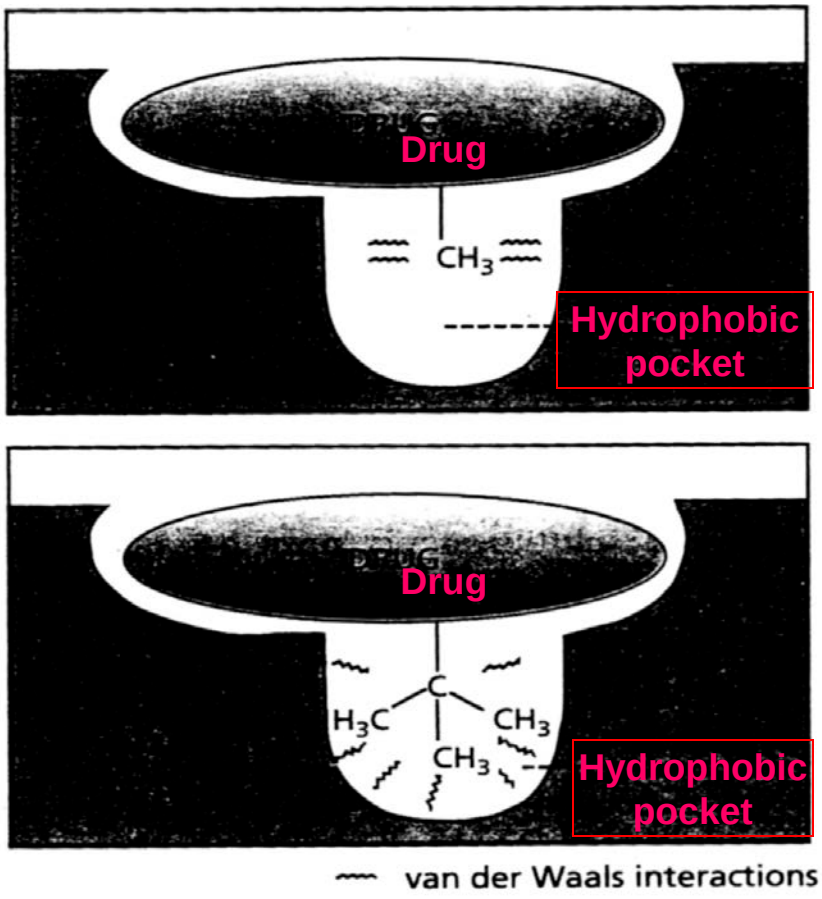


Figure 10.34 Variation of alkyl chain to fill a hydrophobic pocket.

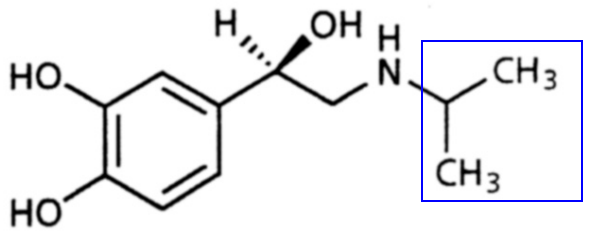
Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

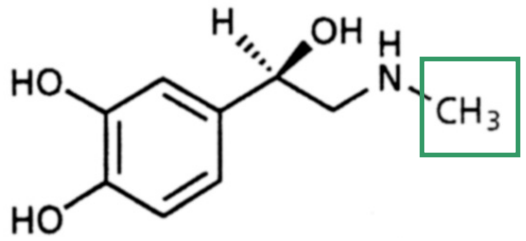
3.1 Variation of substituents

3.1.1 Alkyl substituents

Isoprenaline (Fig. 10.36) is an analogue of adrenaline where a methyl group was replaced by an isopropyl group, resulting in selectivity for adrenergic β-receptors over adrenergic α-receptors .



Isoprenaline



Adrenaline

Figure 10.36 Introducing selectivity for β-adrenoceptors over α-adrenoceptors.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3.1 Variation of substituents

3.1.2 Aromatic substitutions

If a drug contains an aromatic ring, the position of substituents can be varied to find better binding interactions, resulting in increased activity (Fig. 10.37).

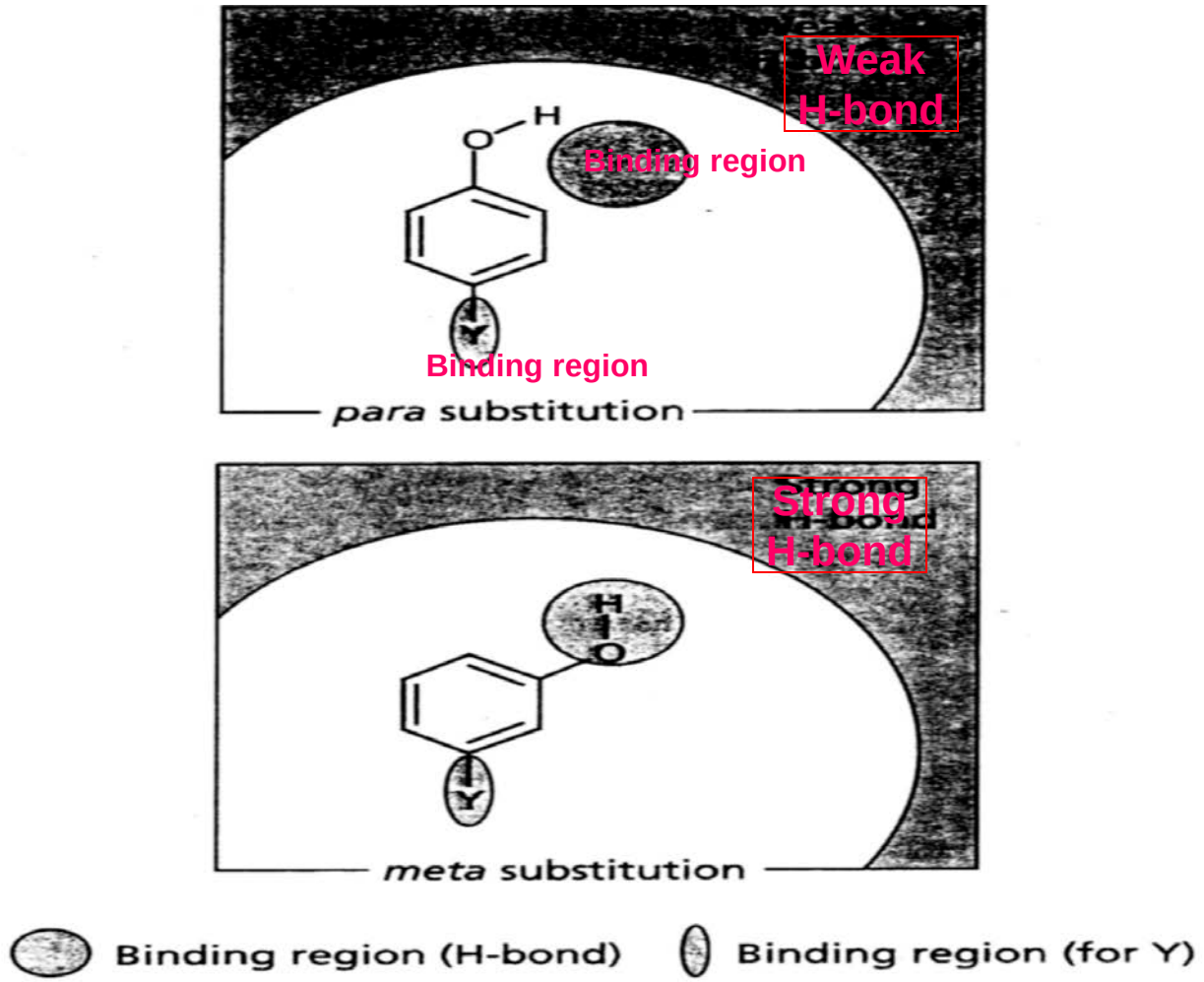


Figure 10.37 Aromatic substitutions.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3.2 Extension of the structure

Extension tactics were used in the development of antihypertensive agents which inhibit an enzyme known as angiotensin-converting enzyme (ACE).

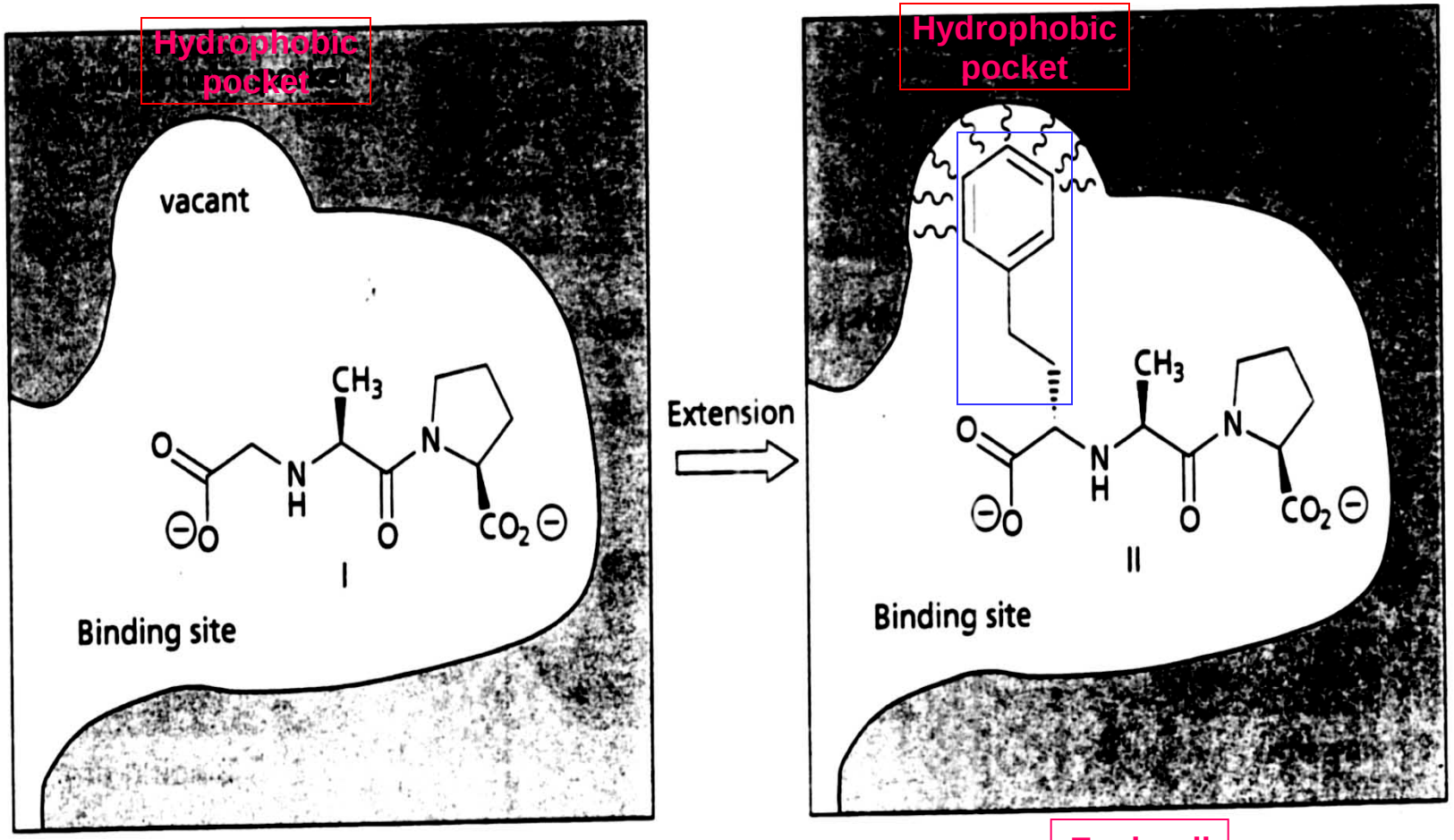
- **Adding a phenylalkyl group to the lead compound (I) increased activity (extension strategy).**
- **Varying the length of the alkyl chain connecting the aromatic ring (11) demonstrated that the phenylethyl group was the best substituent (chain extension strategy).**

This structure showed a 1000-fold improvement in inhibition, demonstrating that the extra aromatic ring was binding to a hydrophobic pocket in the enzyme's active site .

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3.2 Extension of the structure

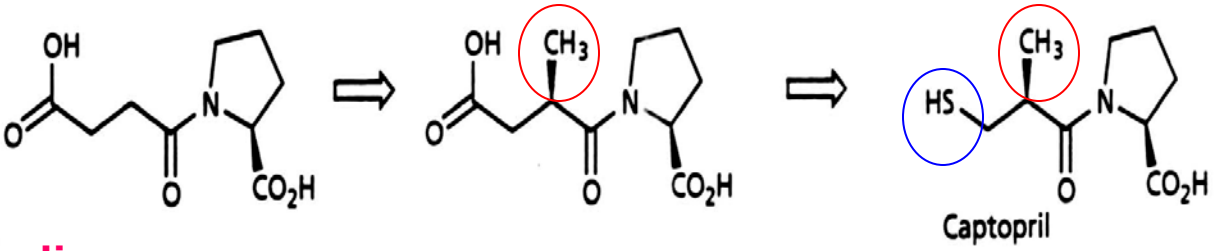


ACE inhibitors.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3.2 Extension of the structure



Increased activity

succinyl proline

Figure 10.65 Development of captopril.

Extension strategies

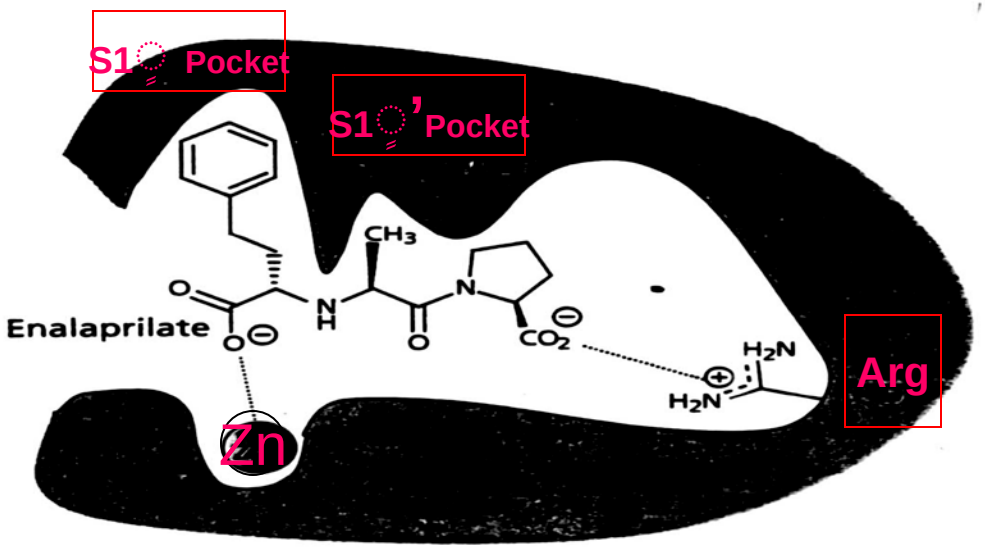


Figure 10.66 Enalaprilate.

binding characteristics using structure-based drug design.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 . 3 Ring variations

1- A popular strategy used for compounds containing an aromatic or heteroaromatic ring is to replace the original ring with a range of other heteroaromatic rings of different

1) ring size and

2) heteroatom positions.

For example,

several non-steroidal anti-inflammatory agents (NSAIDs) have been reported, all consisting of a central ring (thiophen, pyrazol , phenyl …..).with 1,2-biaryl substitution .

Different pharmaceutical companies have varied the central ring to produce a range of active compounds (Fig. 10.44).

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 . 3 Ring variations

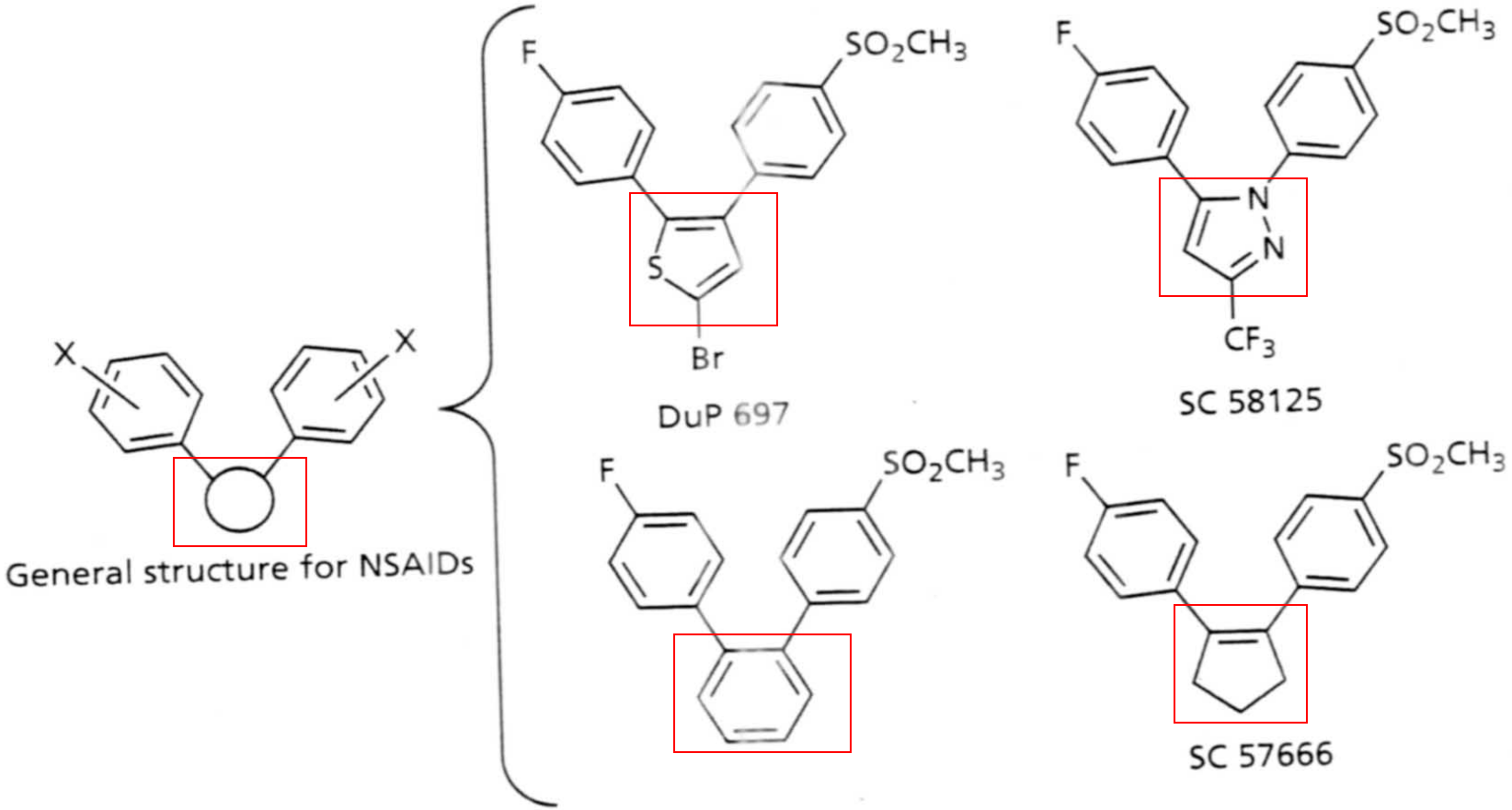


Figure 10.44 Non-steroidal anti-inflammatory drugs (NSAIDS).

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 . 3 Ring variations

2- Admittedly, a lot of these changes are merely ways of avoiding patent restriction,

(me too drugs),

but there can often be significant:

1) improvements in activity, as well as

2) increased selectivity and

3) reduced side effects.

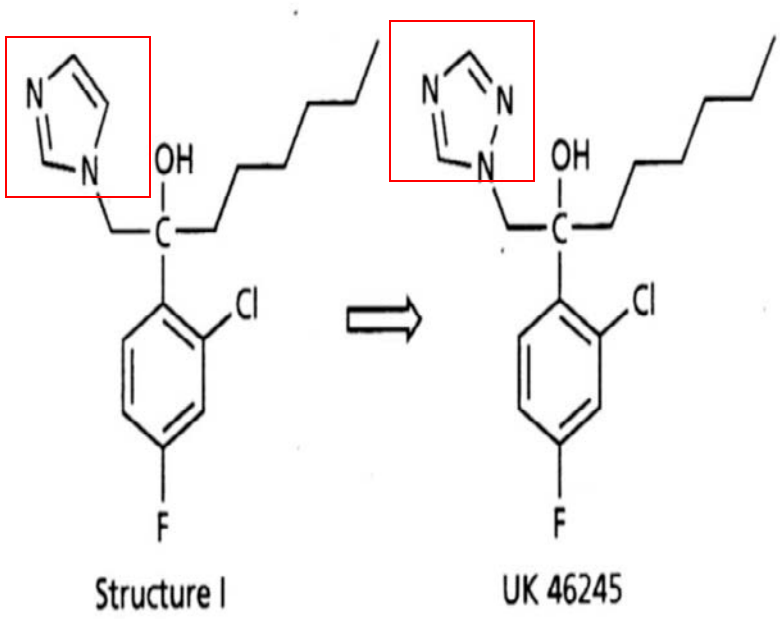


Figure 10.45 Development of UK 46245.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 . 3 Ring variations

For example, the antifungal agent (I) (Fig. 10.45) acts against a fungal enzyme which is also present in humans.

Replacing the imidazole ring of structure (I) with a 1,2,4-triazole ring to give UK 46245 resulted in better selectivity against the fungal form of the enzyme.

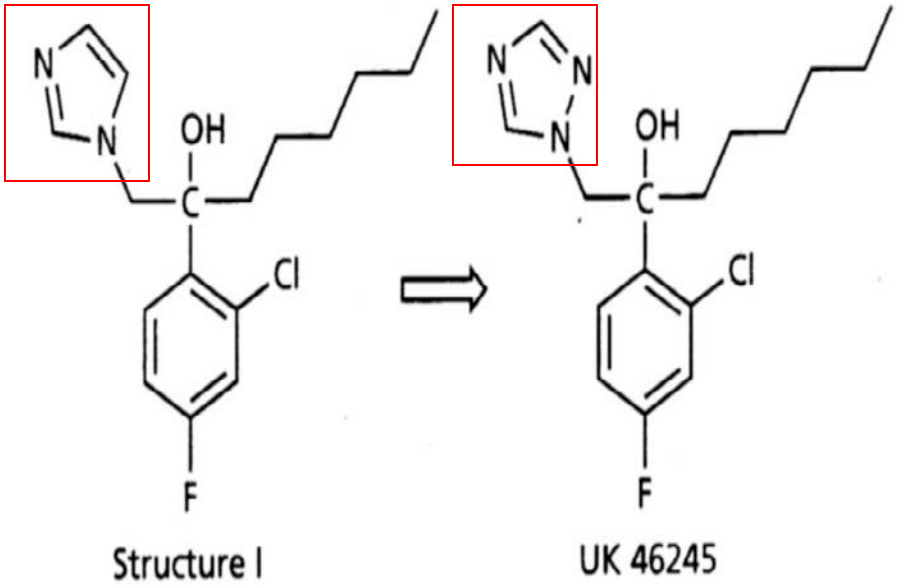


Figure 10.45 Development of UK 46245.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 . 4 Isosteres and bioisosteres

1) Isosteres have often been used in drug design to vary the character of the molecule in a rational way with respect to features such as :

size, polarity, electronic distribution, and bonding:

- **Some isosteres can be used to determine the importance of size towards activity,**
- **whereas others can be used to determine the importance of electronic factors.**

A- For example, fluorine is often used as an isostere of hydrogen since it is virtually the same size. However, it is more electronegative and can be used to vary the electronic properties of the drug without having any steric effect.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 . 4 Isosteres and bioisosteres

B- The presence of fluorine in place of an enzymatically labile hydrogen can also disrupt an enzymatic reaction, as C-F bonds are not easily broken. For example,

the antitumour drug 5-fluorouracil is accepted by its target enzyme because it appears little different from the normal substrate: uracil.

However, the mechanism of the enzyme-catalysed reaction is totally disrupted, as the flourine has replaced a hydrogen which is normally lost during the enzyme mechanism.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 . 4 Isosteres and bioisosteres

2) The term bioisostere is used in drug design and includes both classical and non-classical isosteres (do not obey the steric and electronic rules used to define classical isosteres, but which have similar physical and chemical properties).

a - A bioisostere is a group that can be used to replace another group while retaining the desired biological activity.

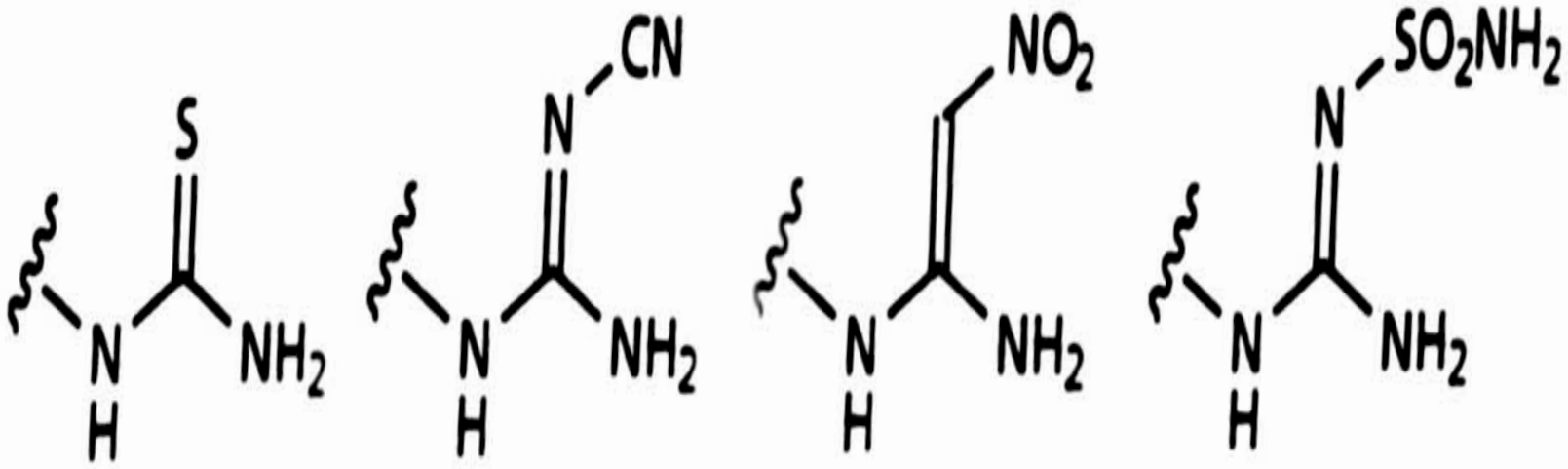
b- Bioisosteres are often used to replace a functional group that is important for target binding but is problematic in one way or another.

For example, the thiourea group was present as an important binding group in early histamine antagonists, but was responsible for toxic side effects. Replacing it with bioisosteres allowed the important binding interactions to be retained for histamine antagonism but avoided the toxicity problems.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 . 4 Isosteres and bioisosteres



Thiourea

Figure 10.48 Non-classical isosteres for a thiourea group.

3 . 4 Isosteres and bioisosteres

c - It is important to realize that bioisosteres are specific for a particular group of compounds and their target.

Replacing a functional group with a bioisostere

is not guaranteed to retain activity for every drug at every target.

d - In some situations, the use of a bioisostere can actually increase target interactions and selectivity.

For example, a pyrrole ring has frequently been used as a non-classical isostere for an amide.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 . 4 Isosteres and bioisosteres

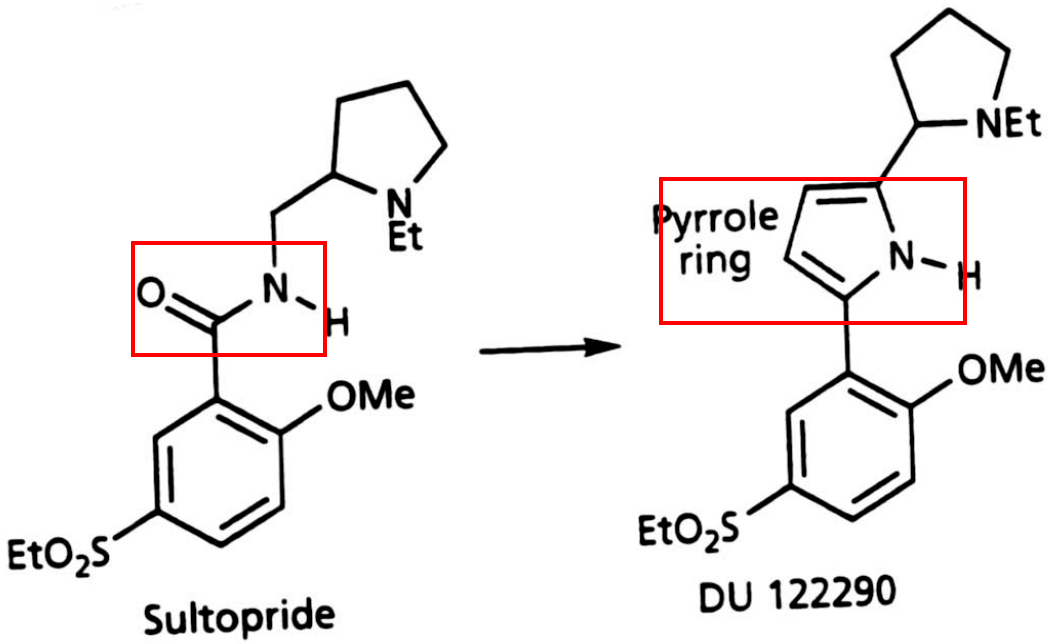


Figure 10.49 Isosteric change for an amide group.

3.5 Simplification of the structure

1) **Simplification is a strategy which is commonly used on the often complex lead compounds arising from natural sources :**

   - Once the essential groups of such a drug have been identified by SAR, it is often possible to discard the non-essential parts of the structure without losing activity.

   - Consideration is given to:
     - removing functional groups which are not part of the pharmacophore,
     - simplifying the carbon skeleton, and
     - removing asymmetric centres.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 . 5 Simplification of the structure

2) **Simplification tactics have been used successfully with the alkaloid cocaine:**

- **Cocaine has local anaesthetic properties, and its simplification led to the development of local anaesthetics which could be easily synthesized in the laboratory.**

  One of the earliest was procaine (Novocaine), discovered in 1909 (Fig. 1).

- **Simplification tactics have also proved effective in the design of simpler morphine analogues (Pethidine).**

- **More recently, the microbial metabolite asperlicin was simplified to devazepide, retaining the benzodiazepine and indole skeletons inherent in the structure (Fig. 2). Both asperlicin and devazepide act as antagonists of a neuropeptide chemical messenger called cholecystokinin (CCK) which has been implicated in causing panic attacks. Therefore, antagonists may be of use in treating such attacks and in the control of appetite.**

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 . 5 Simplification of the structure

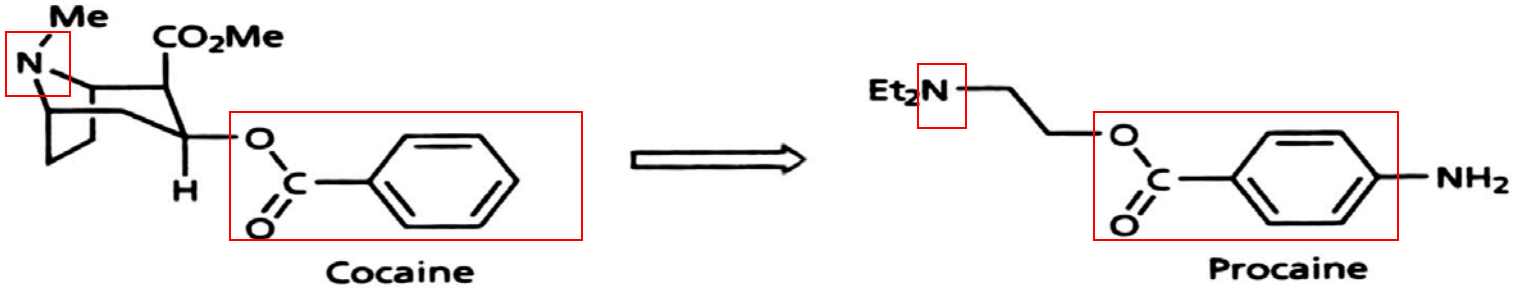


Figure 1 Simplification of cocaine (pharmacophore shown in colour).

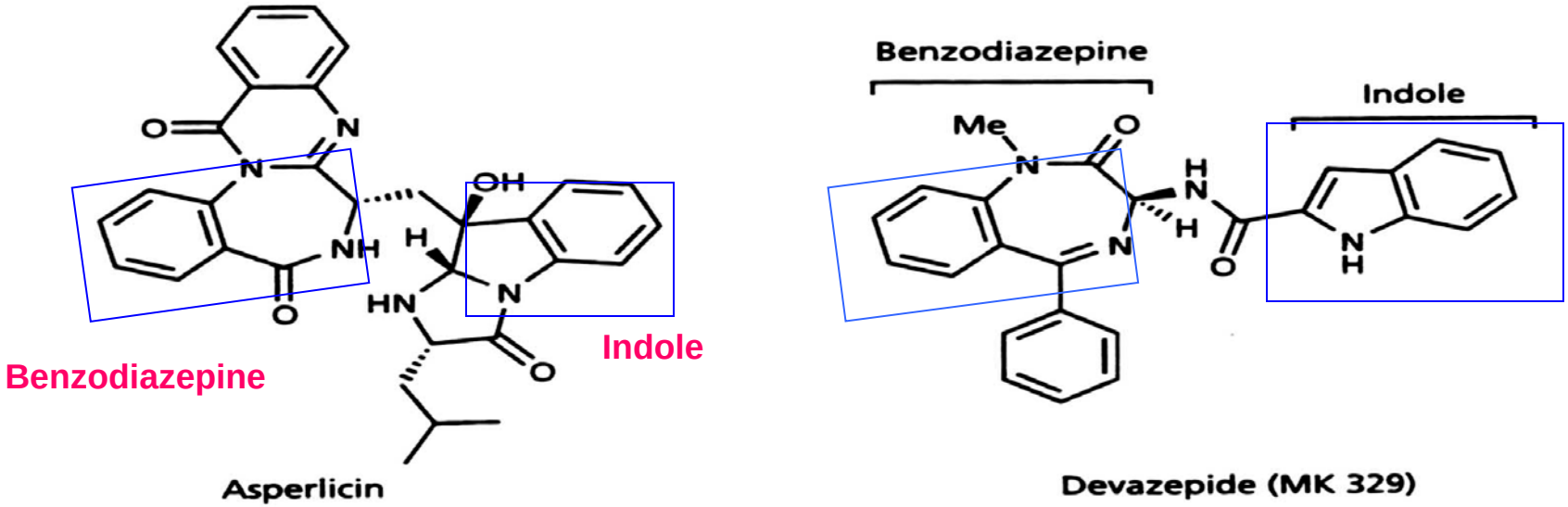


Figure 2 Simplification of asperlicin.

Drug design: optimizing target interactions

1 Structure-activity relationships

1.1 Binding role of alcohols and phenols

1.2 Binding role of aromatic rings

1.3 Binding role of alkenes

1.4 Binding role of ketones and aldehydes

1.5 Binding role of amines

1.6 Binding role of amides

1.7 Binding role of quaternary ammonium salts

1.8 Binding role of carboxylic acids

1.9 Binding role of esters

1.10 Binding role of alkyl and aryl halides

1.11 Binding role of thiols

1.12 Binding role of other functional groups

1.13 Binding role of alkyl groups and the carbon skeleton

1.14 Binding role of heterocycles

1.15 Isosteres

Drug design: optimizing target interactions

2 Identification of a pharmacophore

Drug design: optimizing target interactions

1 Structure-activity relationships

2 Identification of a pharmacophore

3 Drug optimization: strategies in drug design

- 3. 1 Variation of substituents
  - 3.1.1 Alkyl substituents
  - 3.1.2 Aromatic substitutions
- 3. 2 Extension of the structure
- 3 . 3 Ring variations
- 3 . 4 Isosteres and bioisosteres
- 3 . 5 Simplification of the structure

Case study: the design of ACE inhibitors

The design of ACE inhibitors demonstrates how it is possible to design drugs for a protein target in a rational manner even if the structure of the target has not been determined.

The angiotensin-converting enzyme (ACE) is a membrane-bound enzyme which has been difficult to isolate and study.

It is a member of a group of enzymes called the zinc metalloproteinases and catalyses the hydrolysis of a dipeptide fragment from the end of a decapeptide called angiotensin I to give the octapeptide angiotensin II.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 .6 Structure-based drug design and molecular modelling

Case study: the design of ACE inhibitors

Angiotensin II is an important hormone that causes blood vessels to constrict, resulting in a rise in blood pressure.

Therefore, **ACE inhibitors** are potential **antihypertensive agents** because they inhibit the production of **angiotensin II.**

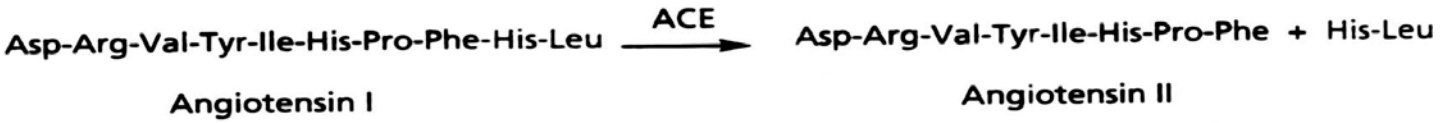


Figure 10.59 Reaction catalysed by ACE.

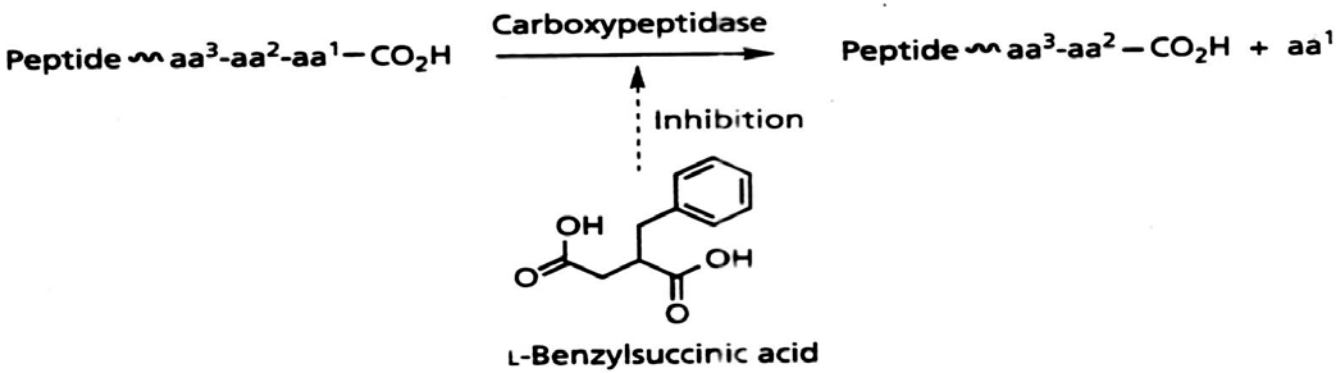


Figure 10.60 Hydrolysis by carboxypeptidase.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 .6 Structure-based drug design and molecular modelling

Case study: the design of ACE inhibitors

Succinyi proline was chosen; since proline is present on the terminus of teprotide (a peptide isolated from the venom of the Brazilian viper, was the lead compound) (a known inhibitor of ACE; Fig. 10.63).

Succinyl proline did indeed inhibit ACE and it was proposed that both carboxylate groups were ionized, one interacting with the arginine group and one with the zinc ion (Fig. 10.64).

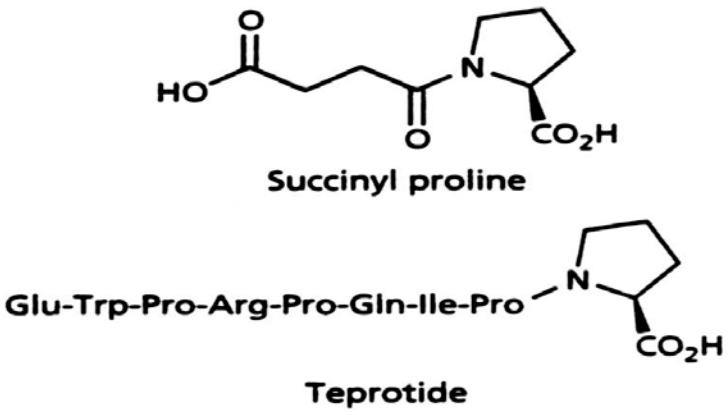


Figure 10.63 ACE inhibitors.

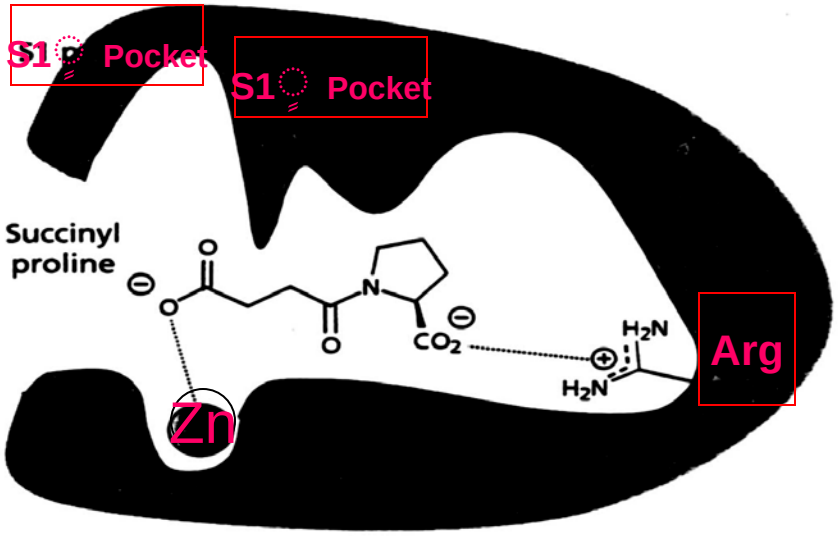


Figure 10.64 Binding site interaction for ACE.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 .6 Structure-based drug design and molecular modelling

Case study: the design of ACE inhibitors

It was now argued that there must be pockets available to accommodate amino acid side chains (pockets S1 and S1').

The strategy of extension was now employed to find a group that would fit the S1' pocket and increase the binding affinity. A methyl group fitted the bill and resulted in an increase in activity (Fig. 10.65).

The next step was to see whether there was a better group than the carboxylate ion to interact with zinc, and it was discovered that a thiol group led to increased activity. This resulted in captopril, which was the first non-peptide ACE inhibitor to become commercially available.

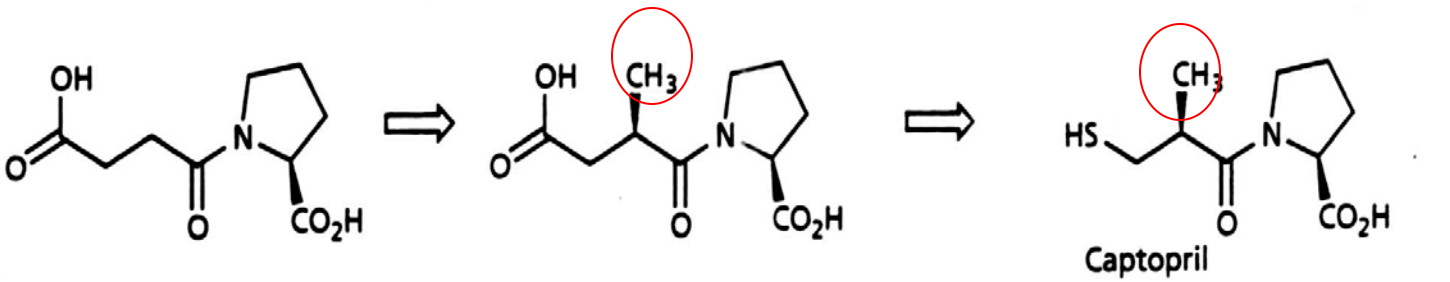


Figure 10.65 Development of captopril.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 .6 Structure-based drug design and molecular modelling

Case study: the design of ACE inhibitors

The next advance involved extension strategies aimed at finding a group that would fit the S 1 pocketnormally occupied by the phenylalanine residue in angiotensin I. This time glutarylproline was used as the lead compound instead of succinyl proline, resulting in the ACE inhibitor enalaprilate (Fig. 10.66).

Extension strategies

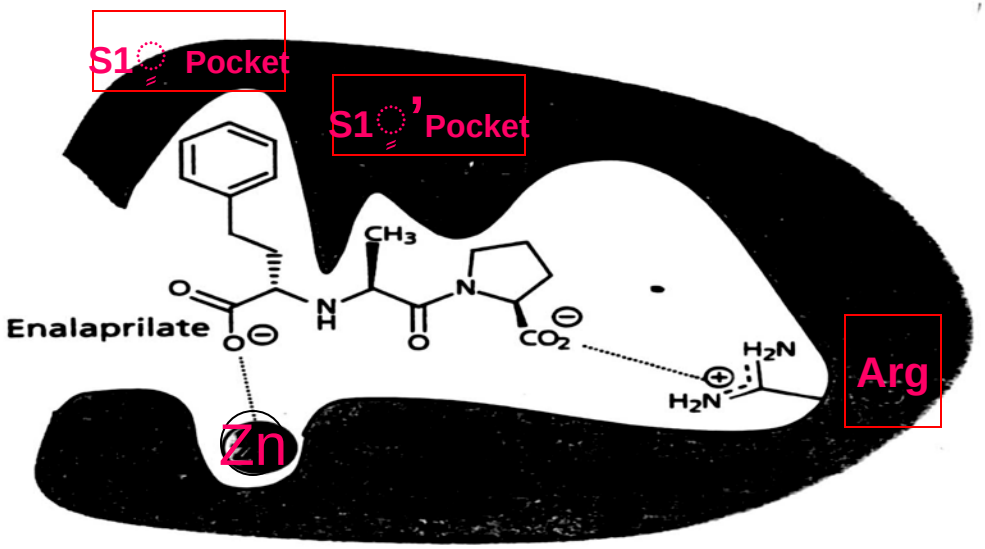


Figure 10.66 Enalaprilate.

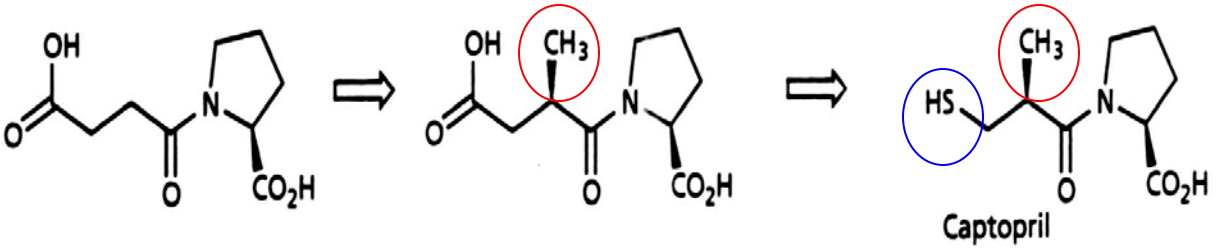
binding characteristics using structure-based drug design.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 .6 Structure-based drug design and molecular modelling

Case study: the design of ACE inhibitors



Increased activity

Figure 10.65 Development of captopril.

Extension strategies

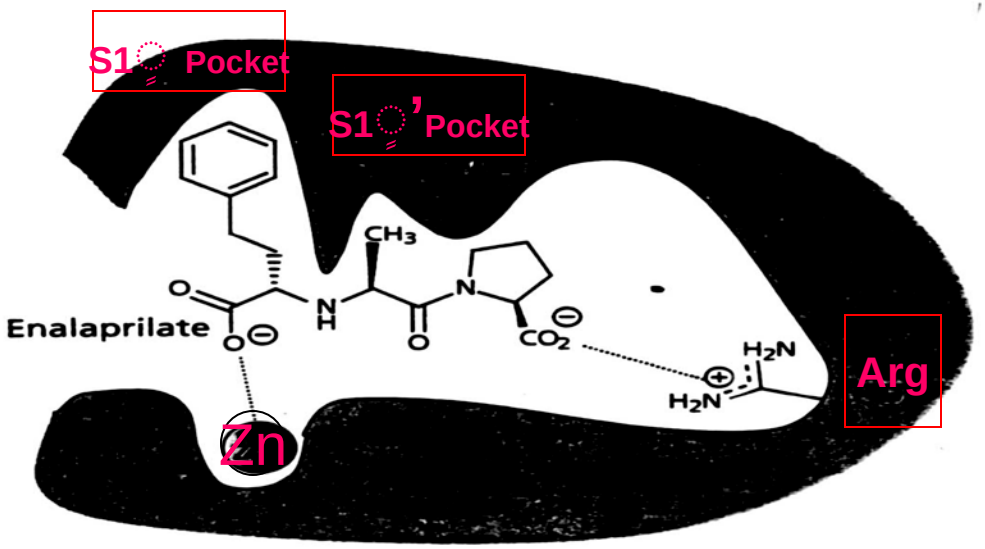


Figure 10.66 Enalaprilate.

binding characteristics using structure-based drug design.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 .6 Structure-based drug design and molecular modelling

Case study: the design of ACE inhibitors

Extension strategies

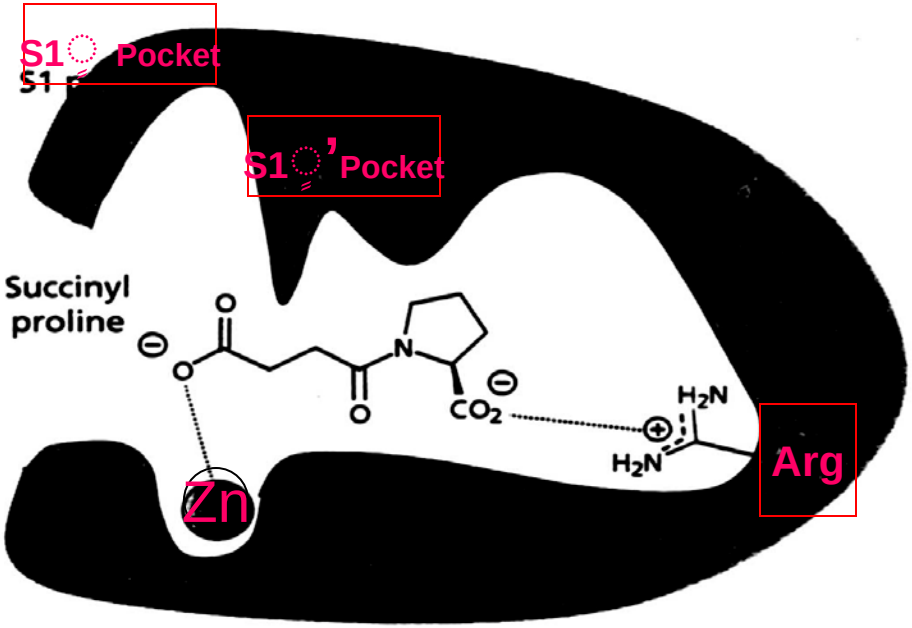


Figure 10.64 Binding site interaction for ACE.

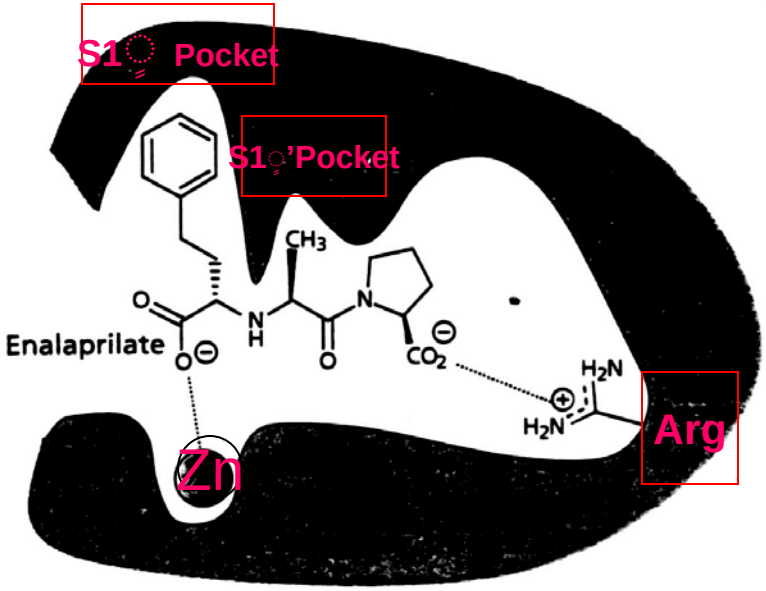


Figure 10.66 Enalaprilate.

binding characteristics using structure-based drug design.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 .6 Structure-based drug design and molecular modelling

Case study: the design of ACE inhibitors

Extension strategies

Drug design: optimizing target interactions

1- Structure-activity relationships

2 - Identification of a pharmacophore

KEY POINTS

1) SARs define the functional groups or regions of a lead compound which are important to its biological activity.

2) Functional groups such as alcohols, amines, esters, amides, carboxylic acids, phenols, and ketones can interact with binding sites by means of hydrogen bonding.

3) Functional groups such as amines, quaternary ammonium salts, and carboxylic acids can interact with binding sites by ionic bonding.

4) Functional groups such as alkenes and aromatic rings can interact with binding sites by means of van der Waals interactions.

Drug design: optimizing target interactions

1- Structure-activity relationships

2 - Identification of a pharmacophore

KEY POINTS

5) Alkyl substituents and the carbon skeleton of the lead compound can interact with hydrophobic regions of binding sites by means of van der Waals interactions.

6) Interactions involving dipole moments or induced dipole moments may play a role in binding a lead compound to a binding site.

7) Reactive functional groups such as alkyl halides may lead to irreversible covalent bonds being formed between a lead compound and its target.

8) The relevance of a functional group to binding can be determined by preparing analogues where the functional group is modified or removed in order to see whether activity is affected by such a change.

Drug design: optimizing target interactions

1- Structure-activity relationships

2 - Identification of a pharmacophore

KEY POINTS

9) Some functional groups can be important to the activity of a lead compound for reasons other than target binding. They may play a role in the electronic or stereochemical properties of the compound, or they may have an important pharmacokinetic role.

10) Replacing a group in the lead compound with an isostere (a group having the same valency) makes it easier to determine whether a particular property such as hydrogen bonding is important.

11) In vitro testing procedures should be used to determine the SAR for target binding.

12) The pharmacophore summarizes the groups which are important in the binding of a lead compound to its target, as well as their relative positions in three dimensions

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

KEY POINTS

- **Drug optimization aims to maximize the interactions of a drug with its target binding site in order to improve activity and selectivity, and to minimize side effects. Designing a drug that can be synthesized efficiently and cheaply is another priority.**

- **The length and size of alkyl substituents can be modified to fill up hydrophobic pockets in the binding site or to introduce selectivity for one target over another. Alkyl groups attached to heteroatoms are most easily modified.**

- **Aromatic substituents can be varied in character and/or ring position.**

KEY POINTS

- **Extension is a strategy where extra functional groups are added to the lead compound in order to interact with extra binding regions in the binding site.**

- **Chains connecting two important binding groups can be modified in length in order to maximize the interactions of each group with the corresponding binding regions.**

- **Rings linking important binding groups can be expanded or contracted such that the binding groups bind efficiently with relevant binding regions.**

Drug design: optimizing target interactions

1 Structure-activity relationships

Drug design: optimizing target interactions

2 Identification of a pharmacophore

Drug design: optimizing target interactions

1 Structure-activity relationships

2 Identification of a pharmacophore

3 Drug optimization: strategies in drug design

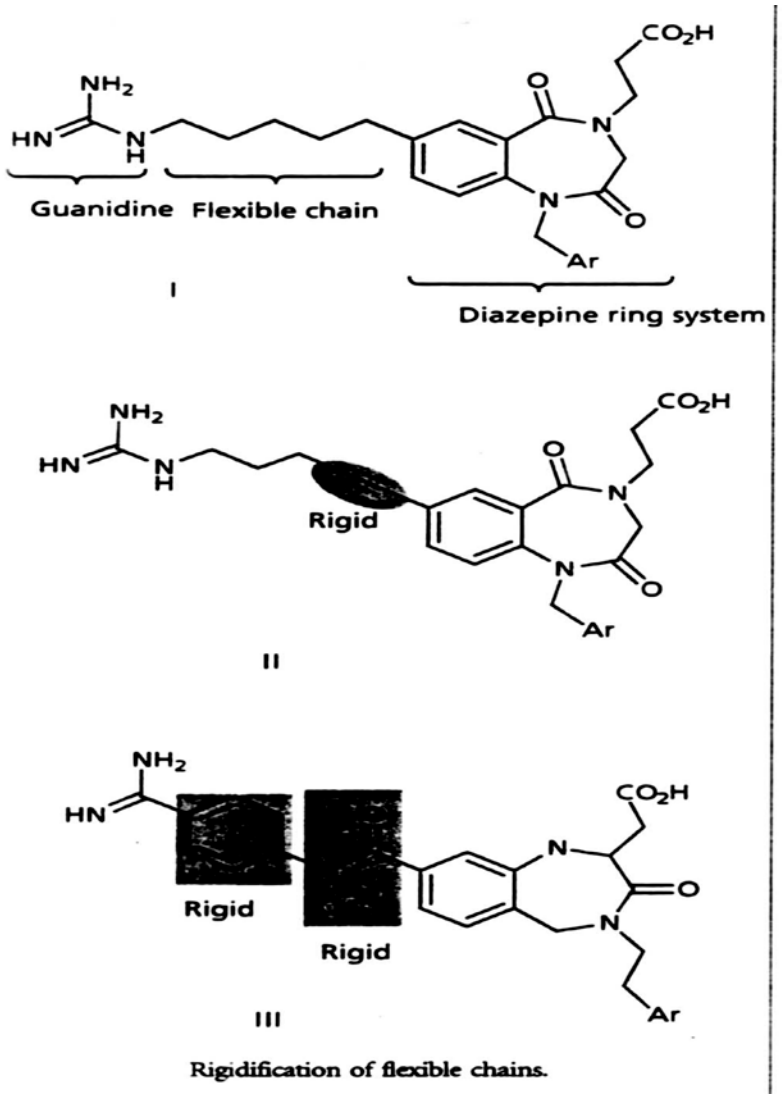
- 3. 1 Variation of substituents
  - 3.1.1 Alkyl substituents
  - 3.1.2 Aromatic substitutions
- 3. 2 Extension of the structure
- 3 . 3 Ring variations
- 3 . 4 Isosteres and bioisosteres
- 3 . 5 Simplification of the structure
- 3 . 6 Structure-based drug design and molecular modelling

Drug design: optimizing target interactions

1 Structure-activity relationships

1.12 Binding role of other functional groups

(Box 10.3).



Rigidification of flexible chains.

Drug design: optimizing target interactions

2 Identification of a pharmacophore

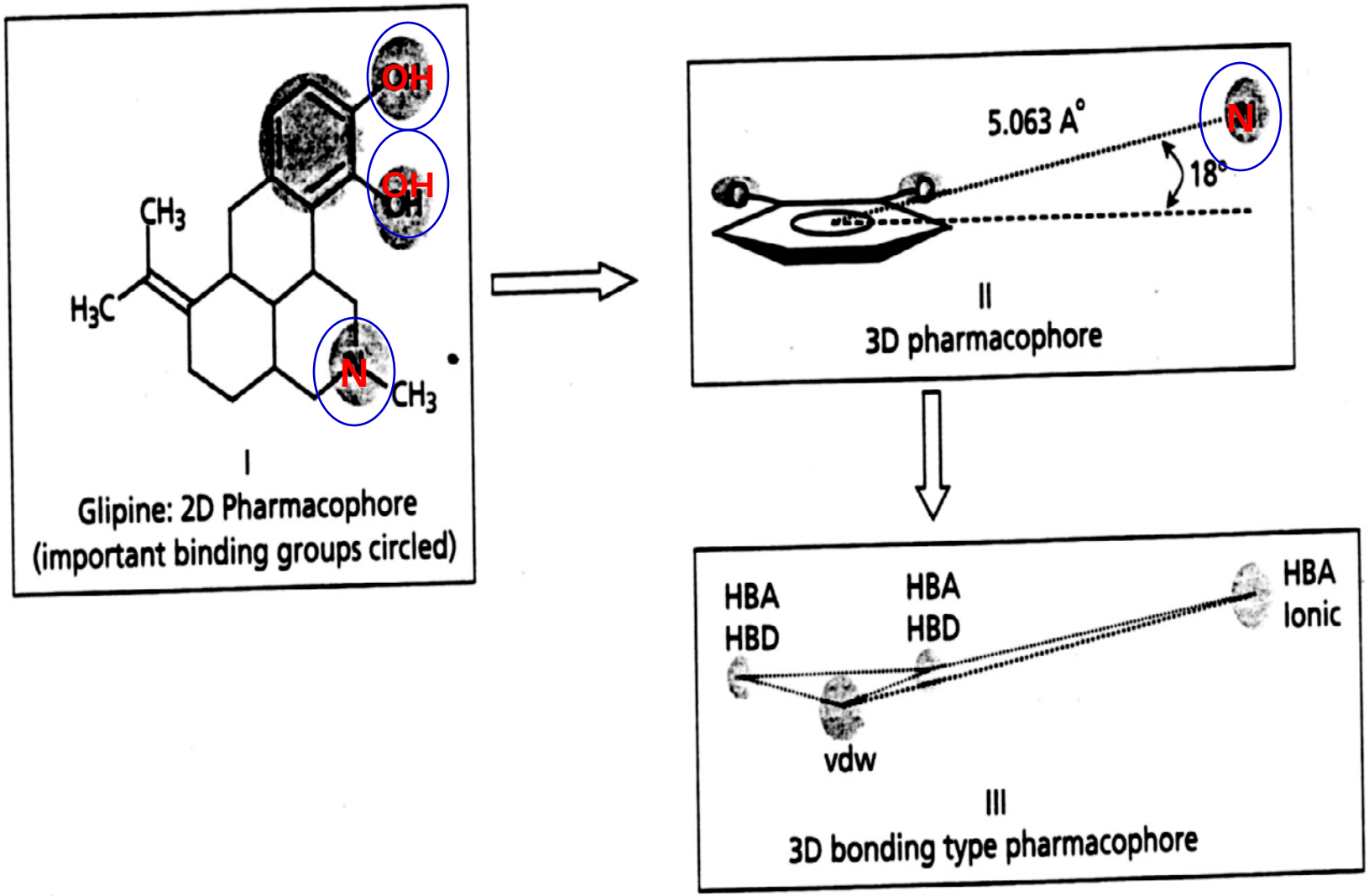


Figure 10.32 A pharmacophore for glipine.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 . 4 Isosteres and bioisosteres

C- Several non-classical isosteres have been used in drug design as replacements for particular functional groups.

Non-classical isosteres are groups which do not obey the steric and electronic rules used to define classical isosteres, but which have similar physical and chemical properties.

For example, the structures shown in Fig. 10.48 are non-classical isosteres for a thiourea group. They are all planar groups of similar size and basicity.

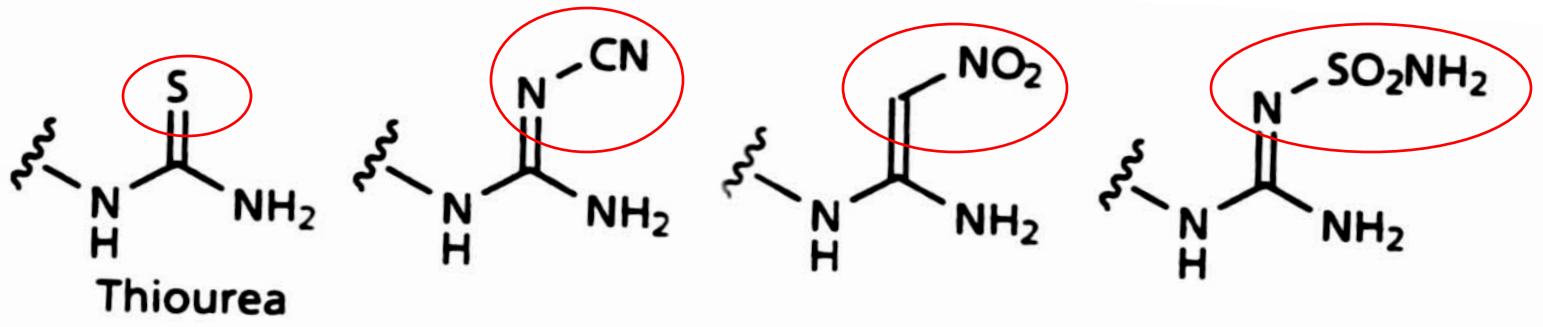


Figure 10.48 Non-classical isosteres for a thiourea group.

Drug design: optimizing target interactions

3 Drug optimization: strategies in drug design

3 . 4 Isosteres and bioisosteres

Carrying out this replacement on the dopamine antagonist sultopride - led to increased activity and selectivity towards the dopamine D_3 receptor over the dopamine D_2 receptor (Fig. 10.49).

Such agents show promise as antipsychotic agents which lack the side effects associated with the D_2 receptor.

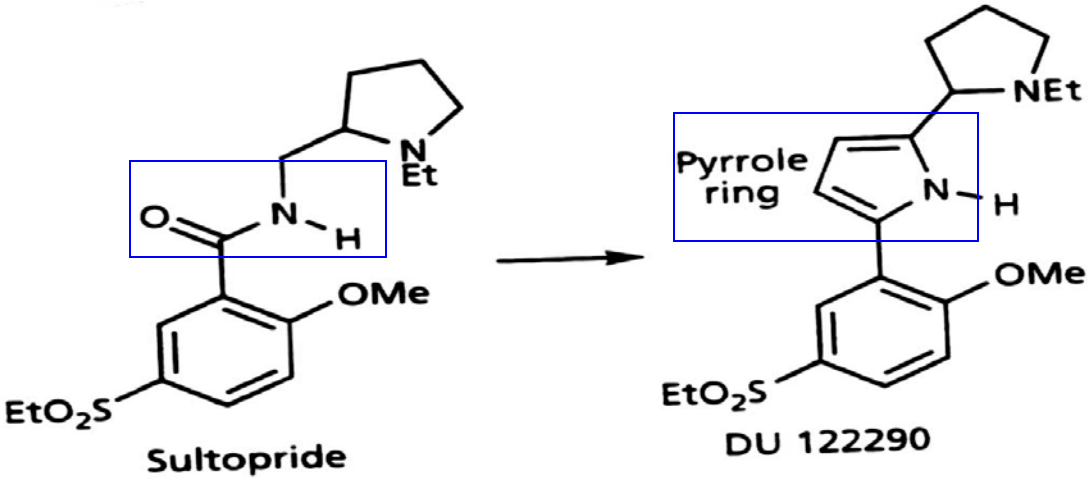


Figure 10.49 Isosteric change for an amide group.