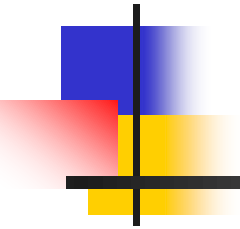
Medicinal Chemistry

Dr. Shuaib Alahmad



Drug Design

Binding Interactions

Binding Interactions

- the binding interactions that are possible for different functional groups and the analogues that could be synthesized to establish whether they are involved in binding or not :

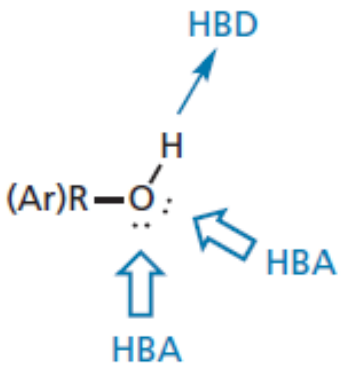
1. Binding role of alcohols and phenols
2. Binding role of aromatic rings
3. Binding role of alkenes
4. binding role of ketones and aldehydes
5. Binding role of amines
6. Binding role of amides
7. Binding role of quaternary ammonium salts

Binding Interactions

8. Binding role of carboxylic acids
9. Binding role of esters
10. Binding role of alkyl and aryl halides
11. Binding role of thiols and ethers
12. Binding role of alkyl groups and the carbon skeleton
13. Binding role of heterocycles
14. Binding role of other functional groups

Binding role of alcohols and phenols

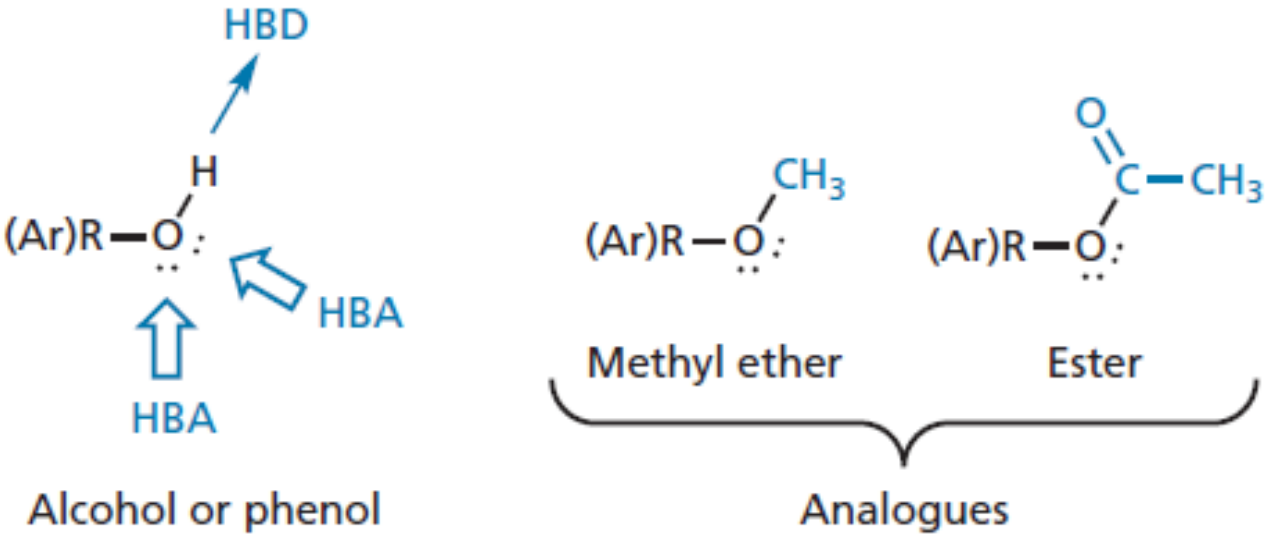
- Alcohols and phenols are functional groups which are commonly present in drugs and are often involved in hydrogen bonding.
- The oxygen can act as a hydrogen bond acceptor, and the hydrogen can act as a hydrogen bond donor.
- One, or all, of these interactions may be important in binding the drug to the binding site.



Alcohol or phenol

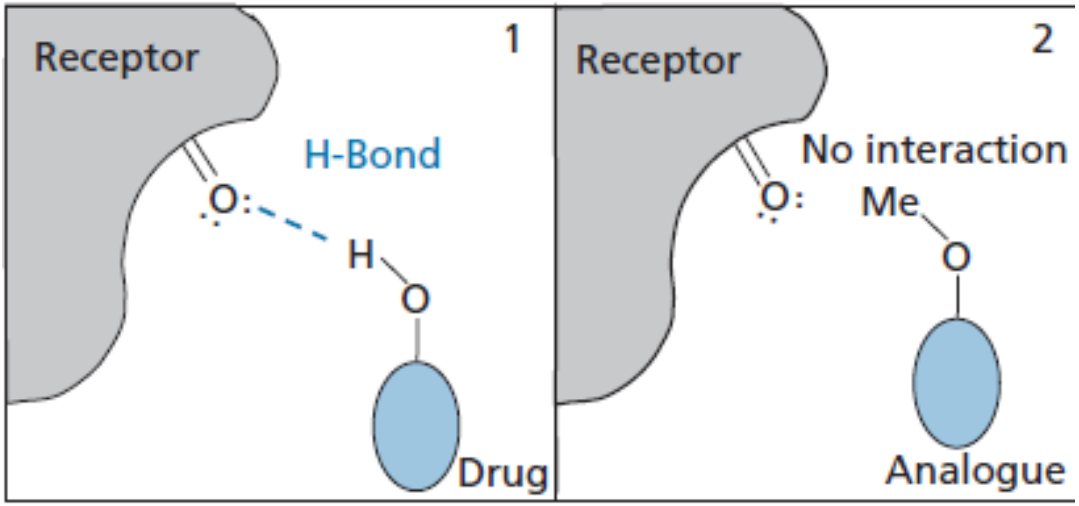
Binding role of alcohols and phenols

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



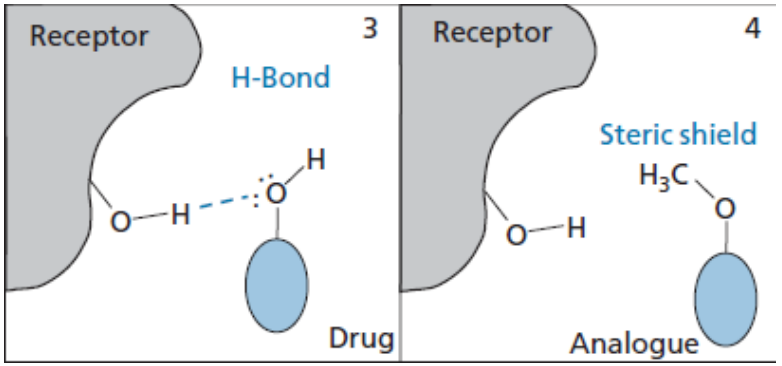
Binding role of alcohols and phenols

- There are two reasons why the ether might hinder or prevent the hydrogen bonding of the original alcohol or phenol.
- The obvious explanation is that the proton of the original hydroxyl group is involved as a hydrogen bond donor and, by removing it, the hydrogen bond is lost



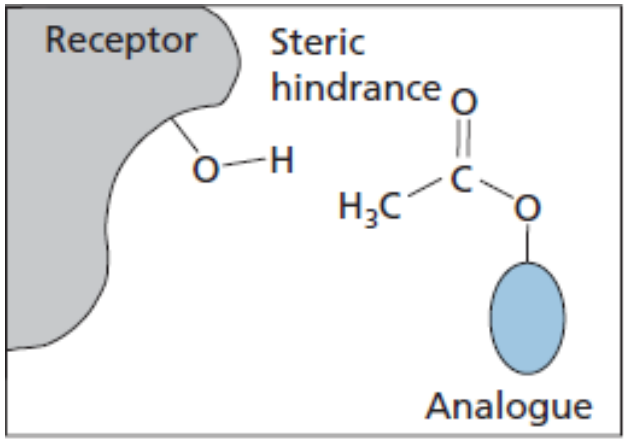
Binding role of alcohols and phenols

- The oxygen is still present in the ether analogue, so it could still take part in hydrogen bonding but possibly not to the same extent.
- The extra bulk of the methyl group should hinder the close approach that was previously attainable and is likely to disrupt hydrogen bonding
- The hydrogen bonding may not be completely prevented, but we could reasonably expect it to be weakened.



Binding role of alcohols and phenols

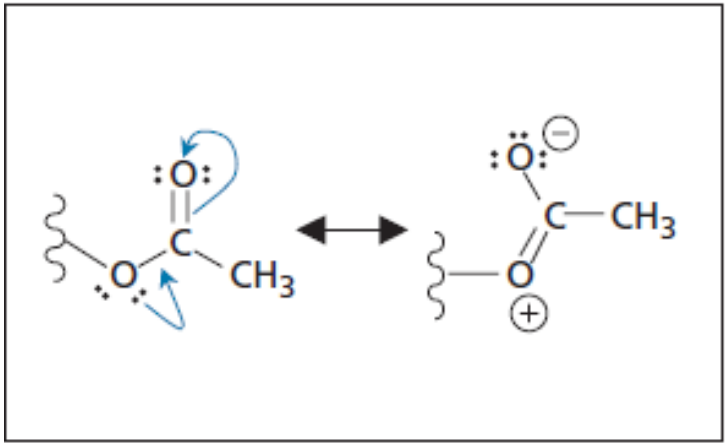
- An ester analogue cannot act as a hydrogen bond donor either.
- There is still the possibility of it acting as a hydrogen bond acceptor, but the extra bulk of the acyl group is even greater than the methyl group of the ether, and this, too, should hinder the original hydrogen bonding interaction.



Steric factor

Binding role of alcohols and phenols

- There is also a difference between the electronic properties of an ester and an alcohol.
- The carboxyl group has a weak pull on the electrons from the neighbouring oxygen, giving the resonance structure
- Because the lone pair is involved in such an interaction, it will be less effective as a hydrogen bond acceptor.



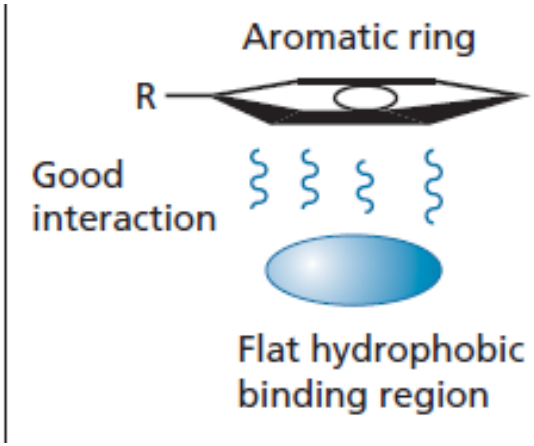
Electronic factor

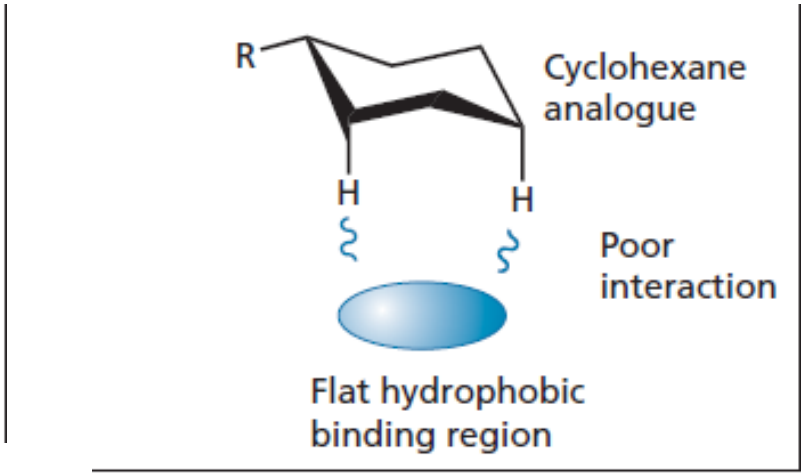
Binding role of alcohols and phenols

- Of course, one could then argue that the carbonyl oxygen is potentially a more effective hydrogen bond acceptor; however, it is in a different position relative to the rest of the molecule and may be poorly positioned to form an effective hydrogen bond interaction with the target binding region.
- It is relatively easy to acetylate alcohols and phenols to their corresponding esters, and this was one of the early reactions that was carried out on natural products such as morphine.
- Alcohols and phenols can also be converted easily to ethers.

Binding role of aromatic rings

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



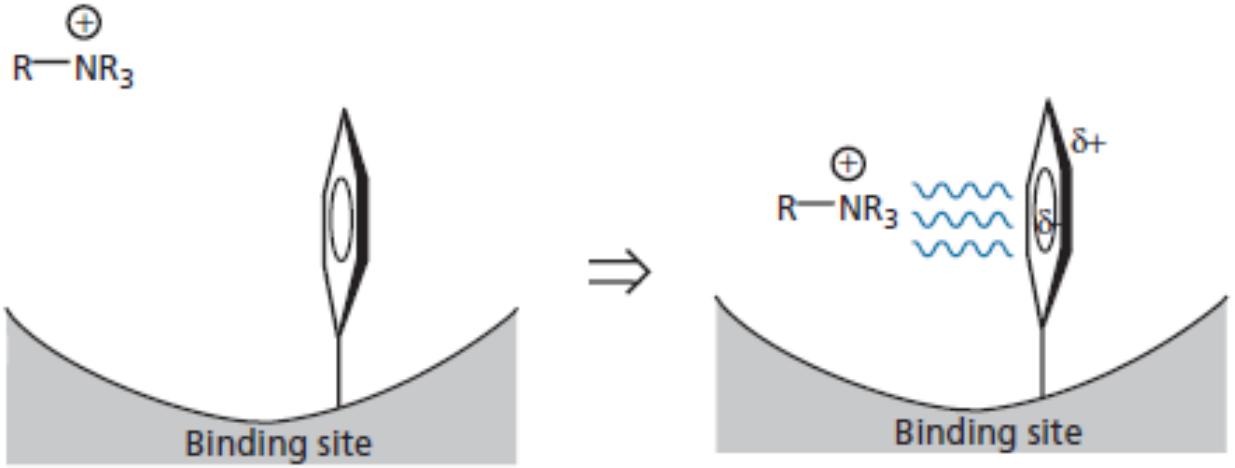


Binding role of aromatic rings

- The axial protons can interact weakly, but they also serve as buffers to keep the rest of the cyclohexane ring at a distance.
- The binding region for the aromatic ring may also be a narrow slot rather than a planar surface.
- In that scenario, the cyclohexane ring would be incapable of fitting into it, because it is a bulkier structure.
- Although there are methods of converting aromatic rings to cyclohexane rings, they are unlikely to be successful with most lead compounds, and so such analogues would normally be prepared using a full synthesis.

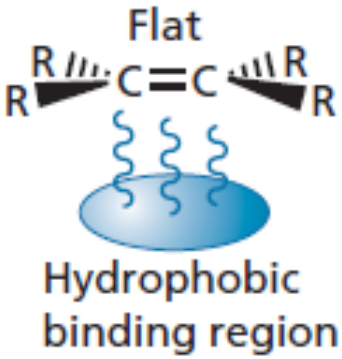
Binding role of aromatic rings

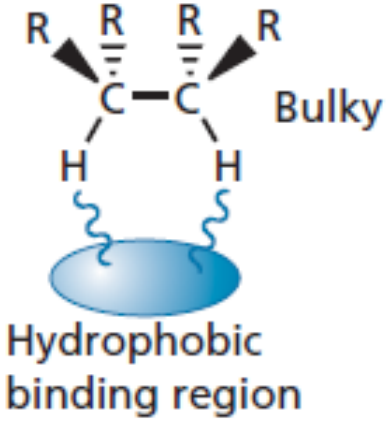
- Aromatic rings could also interact with an aminium or quaternary ammonium ion through induced dipole interactions or hydrogen bonding.
- Such interactions would not be possible for the cyclohexyl analogue.



Binding role of alkenes

- Like aromatic rings, alkenes are planar and hydrophobic so they too can interact with hydrophobic regions of the binding site through van der Waals interactions.
- The activity of the equivalent saturated analogue would be worth testing, as the saturated alkyl region is bulkier and cannot approach the relevant region of the binding site so closely



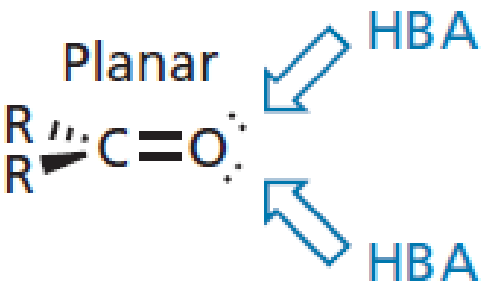


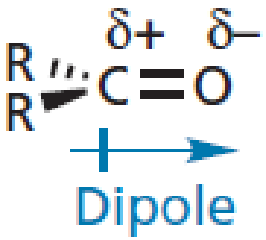
Binding role of alkenes

- Alkenes are generally easier to reduce than aromatic rings, so it may be possible to prepare the saturated analogue directly from the lead compound.

Binding role of ketones and aldehydes

- A ketone group is not uncommon in many of the structures studied in medicinal chemistry.
- 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.
- Two such interactions are possible, as two lone pairs of electrons are available on the carbonyl oxygen.



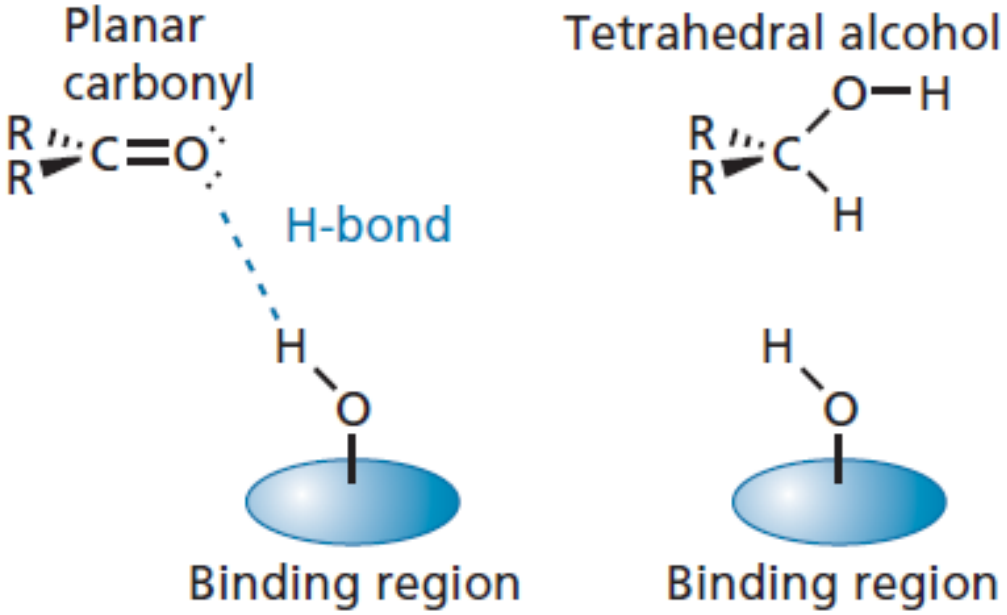


Binding role of ketones and aldehydes

- The lone pairs are in sp2 –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.
- 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.

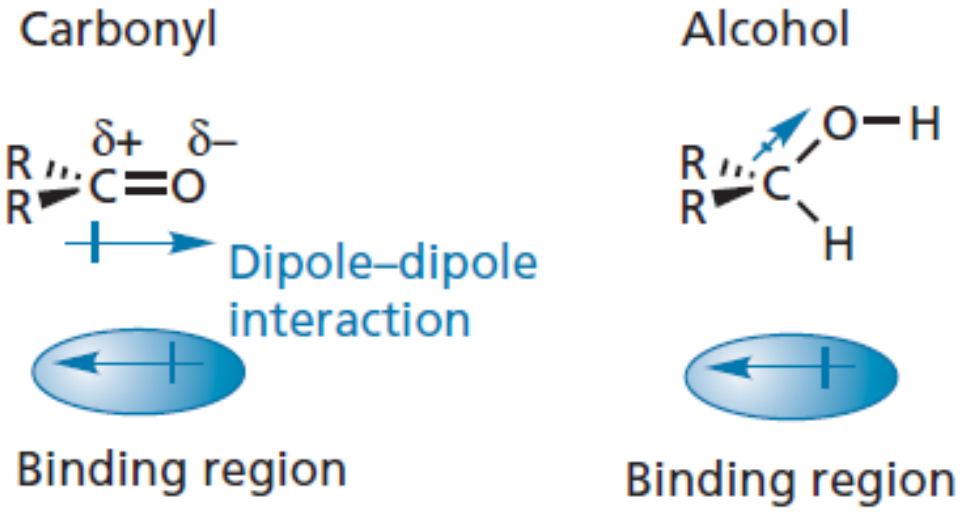
Binding role of ketones and aldehydes

- 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.



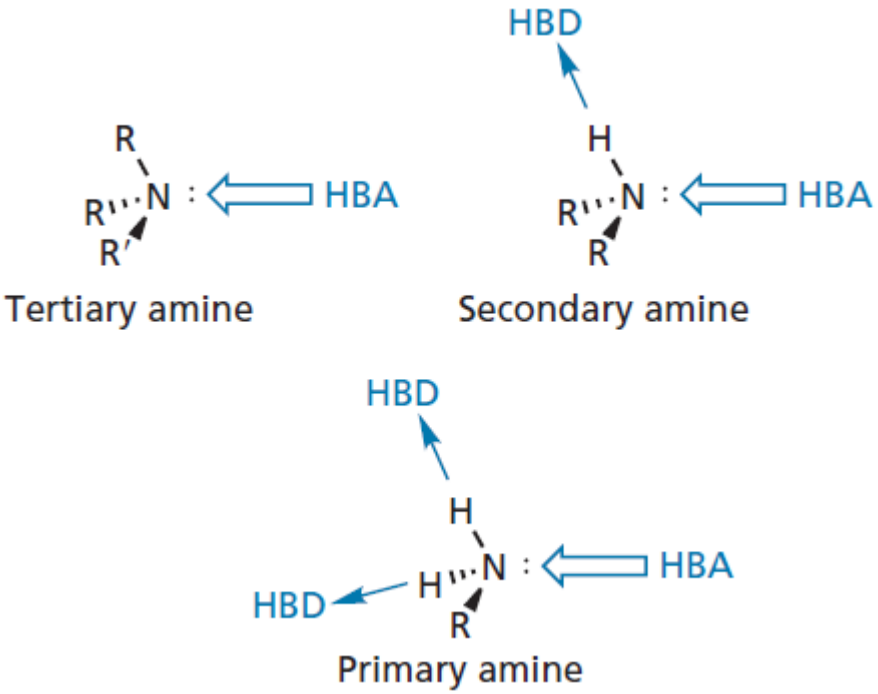
Binding role of ketones and aldehydes

- If it was suspected that the oxygen present in the alcohol analogue might still be acting as a hydrogen bond acceptor, then the ether or ester analogues could be studied as described above.



Binding role of Amines

- Amines are extremely important functional groups in medicinal chemistry and are present in many drugs.
- They may be involved in hydrogen bonding, either as a hydrogen bond acceptor or a hydrogen bond donor.

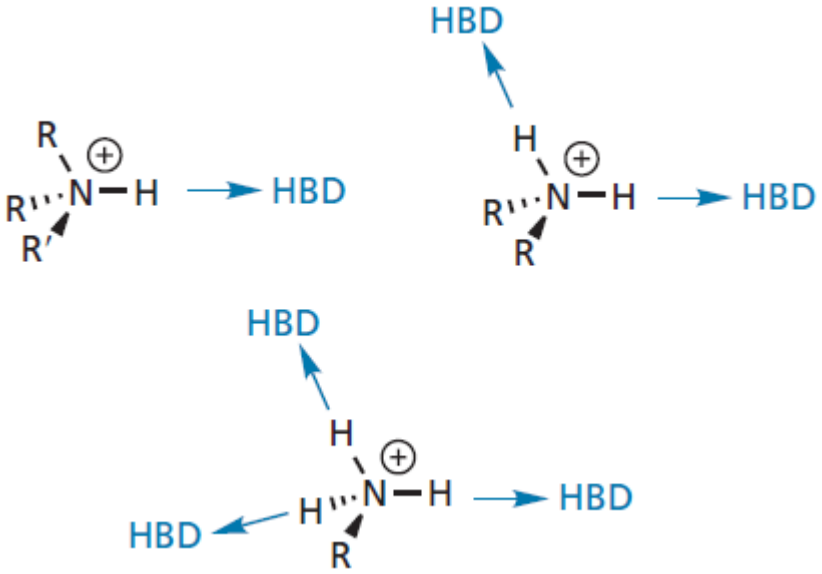


Binding role of Amines

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

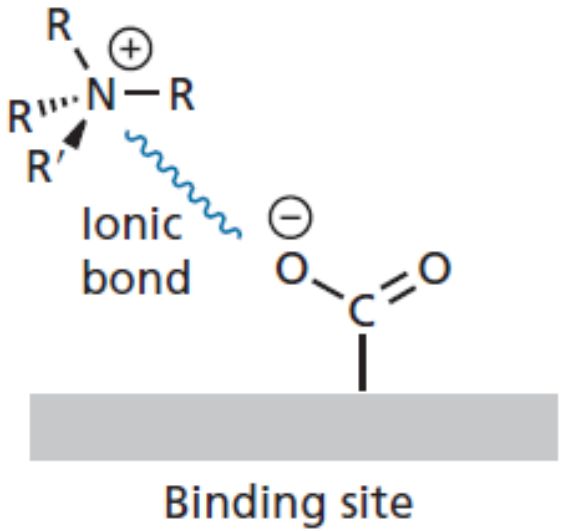
Binding role of Amines

- 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.
- it can still act as a hydrogen bond donor and will form stronger hydrogen bonds than if it was not ionized.



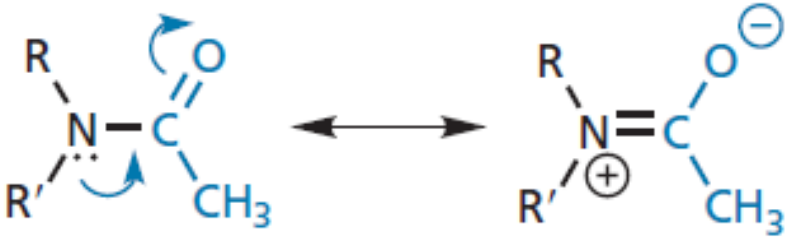
Binding role of Amines

- Alternatively, a strong ionic interaction may take place with a carboxylate ion in the binding site



Binding role of Amines

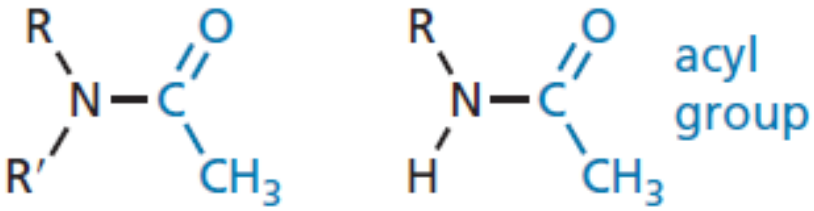
- To test whether ionic or hydrogen bonding interactions are taking place, an amide analogue could be studied.
- This will prevent the nitrogen acting as a hydrogen bond acceptor, as the nitrogen's lone pair will interact with the neighboring carbonyl group instead
- This interaction also prevents protonation of the nitrogen and rules out the possibility of ionic interactions.



N unable to participate in a hydrogen bond or ionic bond

Binding role of Amines

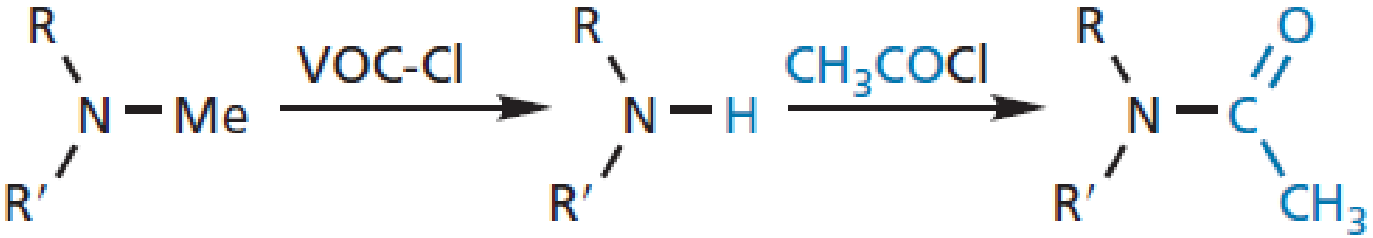
- It is relatively easy to form secondary and tertiary amides from primary and secondary amines, respectively, and it may be possible to carry out this reaction directly on the lead compound.
- A tertiary amide lacks the N–H group of the original secondary amine and would test whether this is involved as a hydrogen bond donor.



Tertiary amide Secondary amide

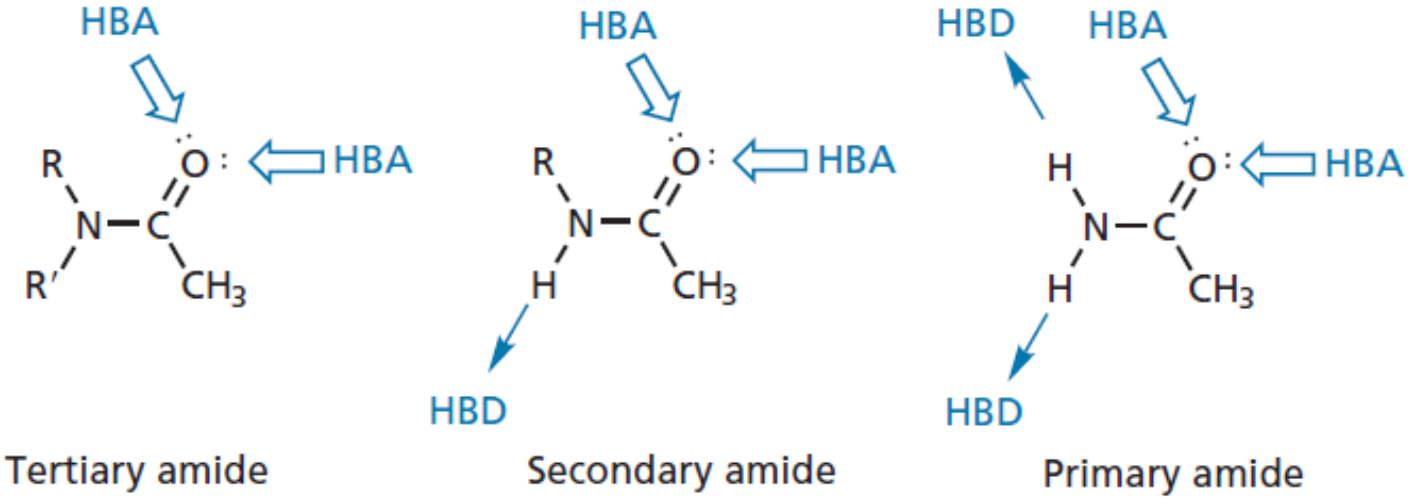
Binding role of Amines

- The secondary amide formed from a primary amine still has a N–H group present, but the steric bulk of the acyl group should hinder it acting as a hydrogen bond donor.
- Tertiary amines cannot be converted directly to amides, but if one of the alkyl groups is a methyl group, it is often possible to remove it with vinyloxycarbonyl chloride (VOC-Cl) to form a secondary amine, which could then be converted to the amide



Binding role of Amide

- Amides are likely to interact with binding sites through hydrogen bonding.
- The carbonyl oxygen atom can act as a hydrogen bond acceptor and has the potential to form two hydrogen bonds.

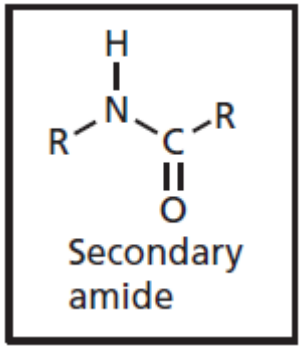


Binding role of Amide

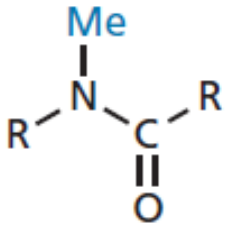
- Both the lone pairs involved are in sp 2 -hybridized orbitals which are located in the same plane as the amide group.
- The nitrogen cannot act as a hydrogen bond acceptor because the lone pair interacts with the neighbouring carbonyl group as described earlier.
- Primary and secondary amides have a N–H group, which allows the possibility of this group acting as a hydrogen bond donor.

Binding role of Amide

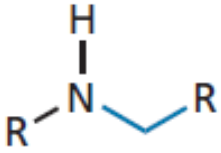
- The most common type of amide in peptide lead compounds is the secondary amide.
- Suitable analogues that could be prepared to test out possible binding interactions are :



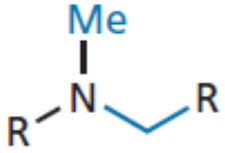
Secondary amide



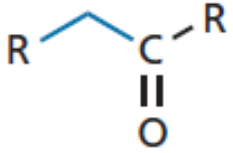
N-Methylated amide



Secondary amine

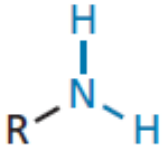


N-Methylated tertiary amine

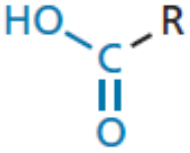


Ketone

Alkene



Primary amine



Carboxylic acid

Binding role of Amide

- All the analogues, apart from the primary and secondary amines, could be used to check whether the amide is acting as a hydrogen bond donor.
- The alkenes and amines could be tested to see whether the amide is acting as a hydrogen bond acceptor.
- However, there are traps for the unwary. The amide group is planar and does not rotate because of its partial double bond character.
- The ketone, the secondary amine, and the tertiary amine analogues have a single bond at the equivalent position which can rotate.

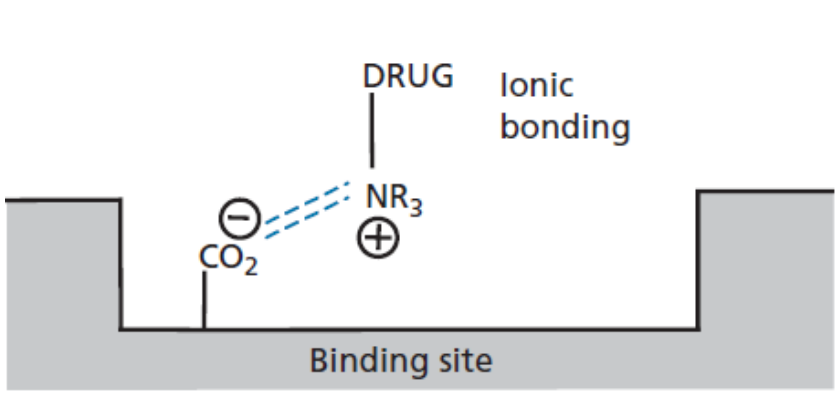
Binding role of Amide

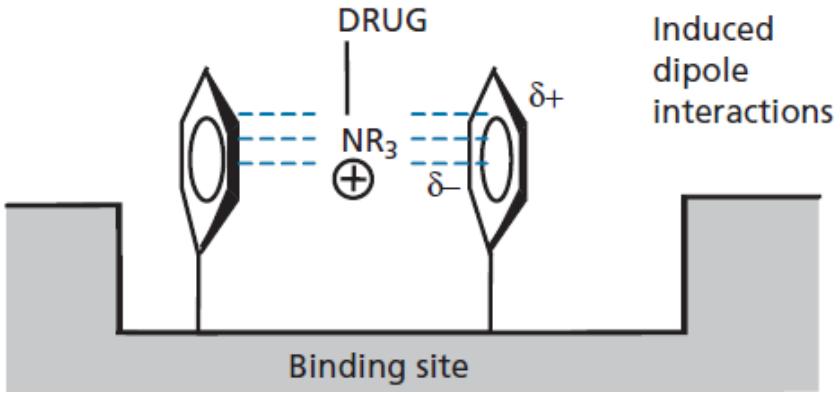
- The alkene would be a particularly useful analogue to test because it is planar, cannot rotate, and cannot act as a hydrogen bond donor or hydrogen bond acceptor.

- the synthesis of this analogue may not be simple. In fact, it is likely that all the analogues described would have to be prepared using a full synthesis.

Binding role of Quaternary ammonium salts

- Quaternary ammonium salts are ionized and can interact with carboxylate groups by ionic interactions.
- Another possibility is an induced dipole interaction between the quaternary ammonium ion and any aromatic rings in the binding site.





Binding role of Quaternary ammonium salts

- The positively charged nitrogen can distort 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.
- This allows an interaction between the slightly negative faces of the aromatic rings and the positive charge of the quaternary ammonium ion.
- This is also known as a π-cation interaction

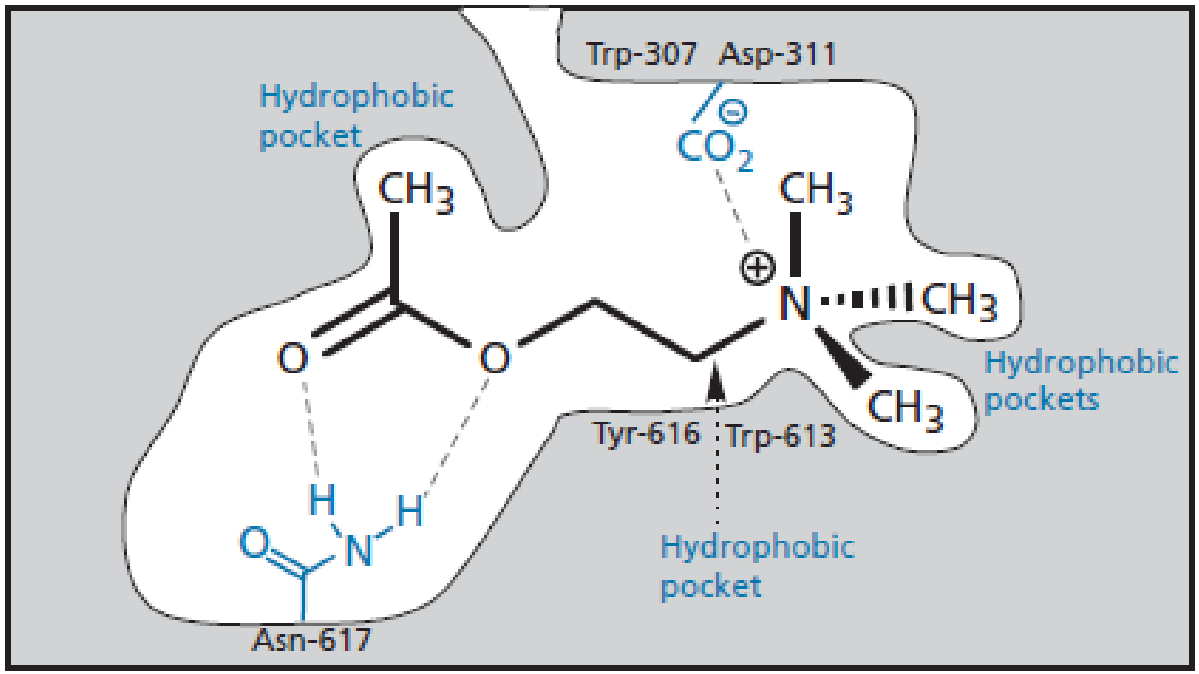
Binding role of Quaternary ammonium salts

- The importance of these interactions could be tested by synthesizing an analogue that has a tertiary amine group rather than the quaternary ammonium group.

- Of course, it is possible that such a group could ionize by becoming protonated and then interact in the same way.
- Converting the amine to an amide would prevent this possibility.

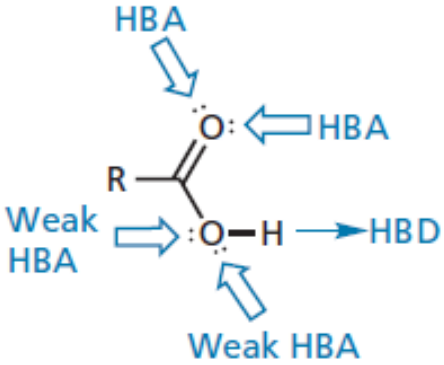
Binding role of Quaternary ammonium salts

- The neurotransmitter **acetylcholine** has a quaternary ammonium group which is thought to bind to the binding site of its target receptor by ionic bonding and/or induced dipole interactions.

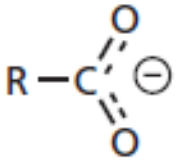


Binding role of Carboxylic Acid

- The carboxylic acid group is reasonably common in drugs.
- It can act as a hydrogen bond acceptor or as a hydrogen bond donor.
- Alternatively, it may exist as the carboxylate ion.
- This allows the possibility of an ionic interaction and/or a strong hydrogen bond where the carboxylate ion acts as the hydrogen bond acceptor.



Carboxylic acid

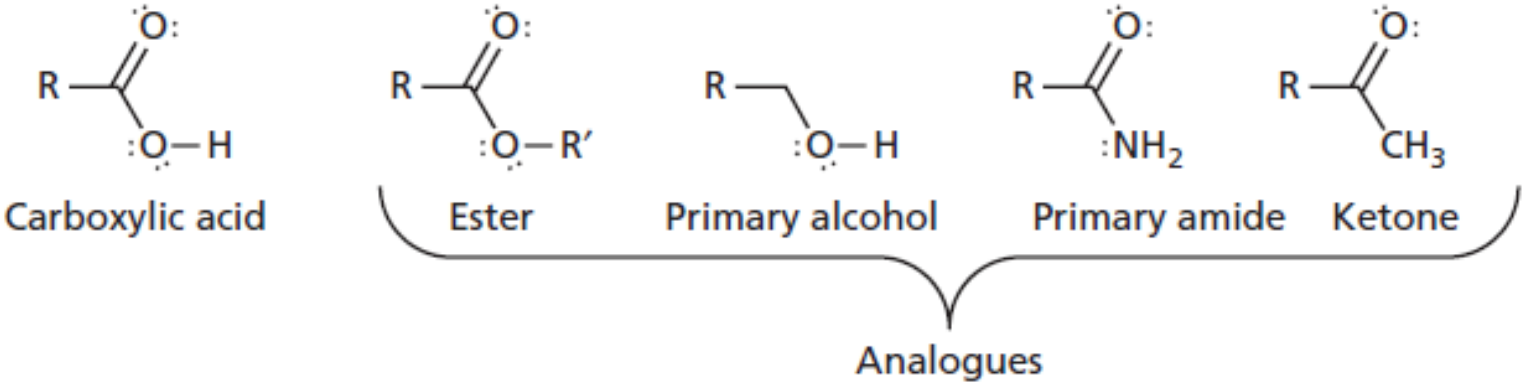


Carboxylate ion

Ionic interaction
and/or
strong hydrogen bond acceptor

Binding role of Carboxylic Acid

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



Binding role of Carboxylic Acid

- 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.
- It may be possible to synthesize the ester and amide analogues directly from the lead compound, but the reduction of a carboxylic acid to a primary alcohol requires harsher conditions and this sort of analogue would normally be prepared by a full synthesis.
- The ketone would also have to be prepared by a full synthesis.

Binding role of Esters

- An ester functional group has the potential to interact with a binding site as a hydrogen bond acceptor only.
- The carbonyl oxygen is more likely to act as the hydrogen bond acceptor than the alkoxy oxygen as it is sterically less hindered and has a greater electron density.

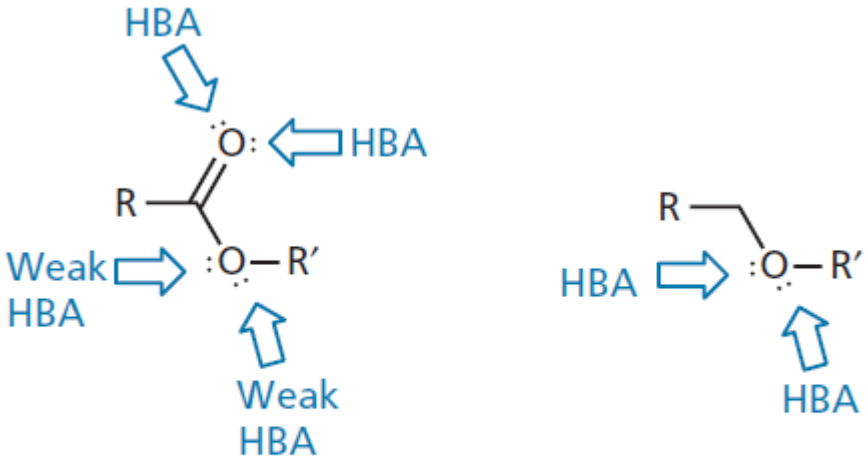


FIGURE 13.21 Possible binding interactions for an ester and an ether.

Binding role of Esters

- The importance of the carbonyl group could be judged by testing an equivalent ether, which would require a full synthesis.
- Esters are susceptible to hydrolysis *in vivo* by metabolic enzymes called esterases .
- 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* .
- There are several drugs that *do* contain esters and are relatively stable to metabolism thanks to electronic factors that stabilize the ester or steric factors that protect it.

Binding role of Esters

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

Binding role of alkyl and aryl halides

- Alkyl halides involving chlorine, bromine, or iodine tend to be chemically reactive as 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 that it encounters and become permanently linked to that group by a covalent bond (an alkylation reaction).
- This poses a problem, as the drug is likely to alkylate a large variety of macromolecules which have

Binding role of alkyl and aryl halides

- This poses a problem, as the drug is likely to alkylate a large variety of macromolecules which have nucleophilic groups, especially amine groups in proteins and nucleic acids.
- It is possible to moderate the reactivity to some extent, but selectivity is still a problem and leads to severe side effects.

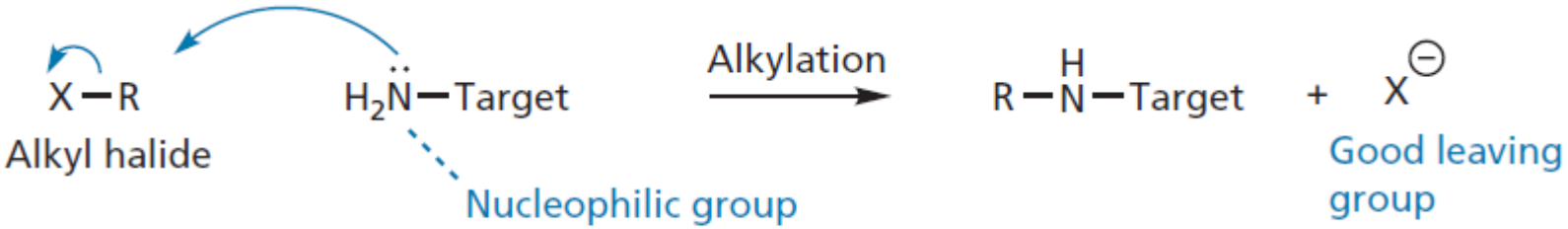
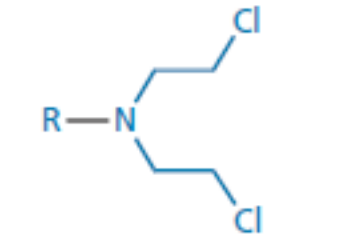


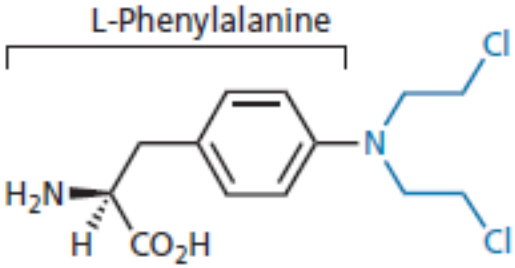
FIGURE 13.23 Alkylation of macromolecular targets by alkyl halides.

Binding role of alkyl and aryl halides

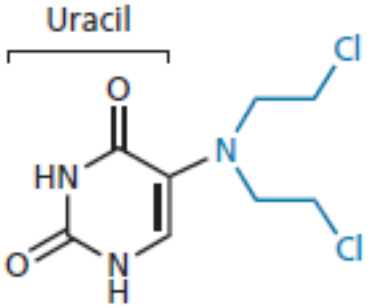
- These drugs are, therefore, reserved for life-threatening diseases, such as cancer.



Chlormethine (R = Me)
Structure I (R = Ph)



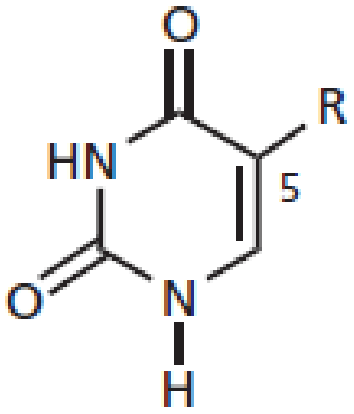
Melphalan
(L-Phenylalanine mustard, L-PAM)



Uracil mustard

Binding role of alkyl and aryl halides

- Alkyl fluorides are not alkylating agents because the C–F bond is strong and 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



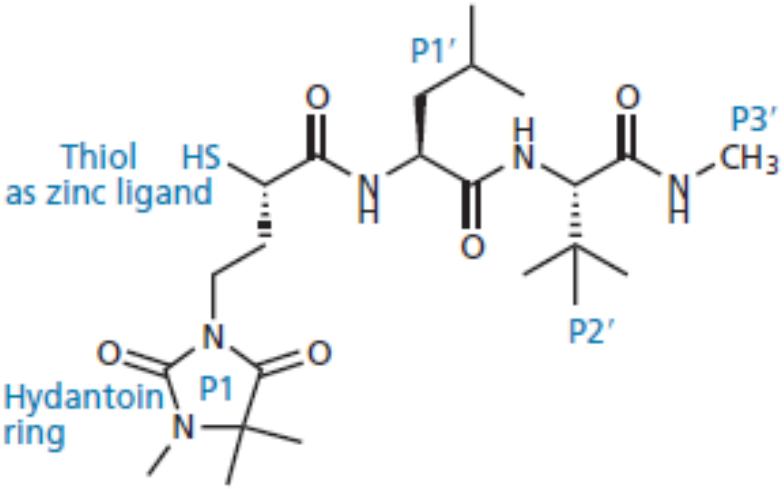
R = H Uracil
R = F 5-Fluorouracil

Binding role of alkyl and aryl halides

- 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.
- The halogen substituents chlorine and bromine are hydrophobic in nature and may interact favourably with hydrophobic pockets in a binding site.
- Hydrogen bonding is not important. Although halide ions are strong hydrogen bond acceptors, halogen substituents are poor hydrogen bond acceptors.

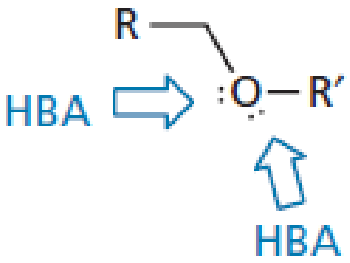
Binding role of thiols and ethers

- The thiol group (-SH) is known to be a good ligand for d-block metal ions and has been incorporated into several drugs designed to inhibit enzymes containing a zinc cofactor, for example the zinc metalloproteinases.
- For example BMS 275291 peptide-like which has a thiol group as the ligand for zinc



Binding role of thiols and ethers

- If the lead compound has a thiol group, the corresponding alcohol could be tested as a comparison. This would have a far weaker interaction with zinc.
- An ether group (R-O-R) might act as a hydrogen bond acceptor through the oxygen atom.



- This could be tested by increasing the size of the neighbouring alkyl group to see whether it diminishes the ability of the group to take part in hydrogen bonding.

Binding role of thiols and ethers

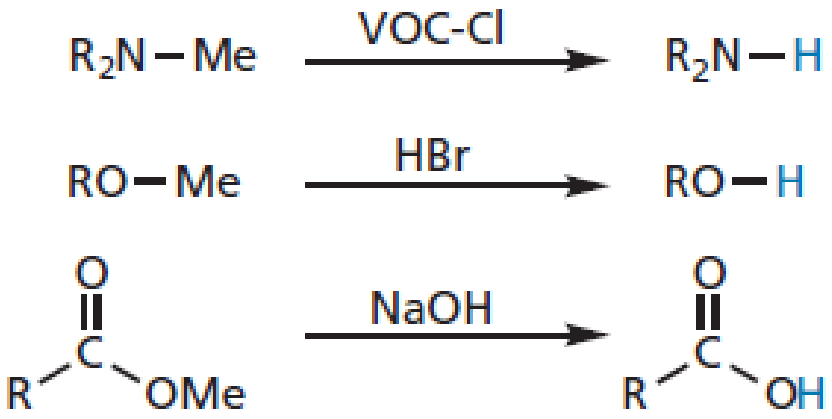
- Analogues where the oxygen is replaced with a methylene (CH_2) isostere should show significantly decreased binding affinity.
- The oxygen atom of an aromatic ether is generally a poor hydrogen bond acceptor.

Binding role of alkyl groups and the carbon skeleton

- 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 interactions.
- The relevance of an alkyl substituent to binding can be determined by synthesizing an analogue which lacks the substituent.
- Such analogues generally have to be synthesized using a full synthesis if they are attached to the carbon skeleton of the molecule.

Binding role of alkyl groups and the carbon skeleton

- if the alkyl group is attached to nitrogen or oxygen, it may be possible to remove the group from the lead compound.



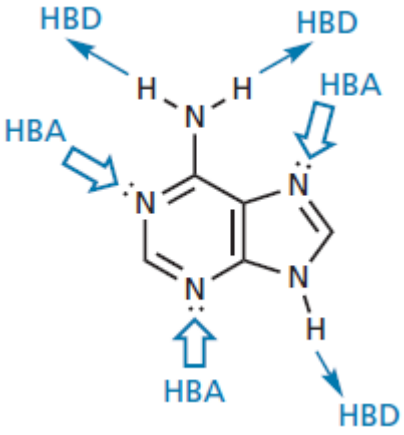
- The analogues obtained may then be expected to have less activity if the alkyl group was involved in important hydrophobic interactions.

Binding role of Heterocycles

- A large diversity of heterocycles are found in lead compounds.
- Heterocycles are cyclic structures that contain one or more heteroatoms, such as oxygen, nitrogen, or sulphur.
- Nitrogen-containing heterocycles 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 heteroatoms present in the structure could interact by hydrogen bonding or ionic bonding.

Binding role of Heterocycles

- As far as hydrogen bonding is concerned, there is an important directional aspect.
- The position of the heteroatom in the ring and the orientation of the ring in the binding site can be crucial in determining whether or not a good interaction takes place.
- For example, adenine can take part in six hydrogen bonding interactions: three as a hydrogen bond donor and three as a hydrogen bond acceptor.



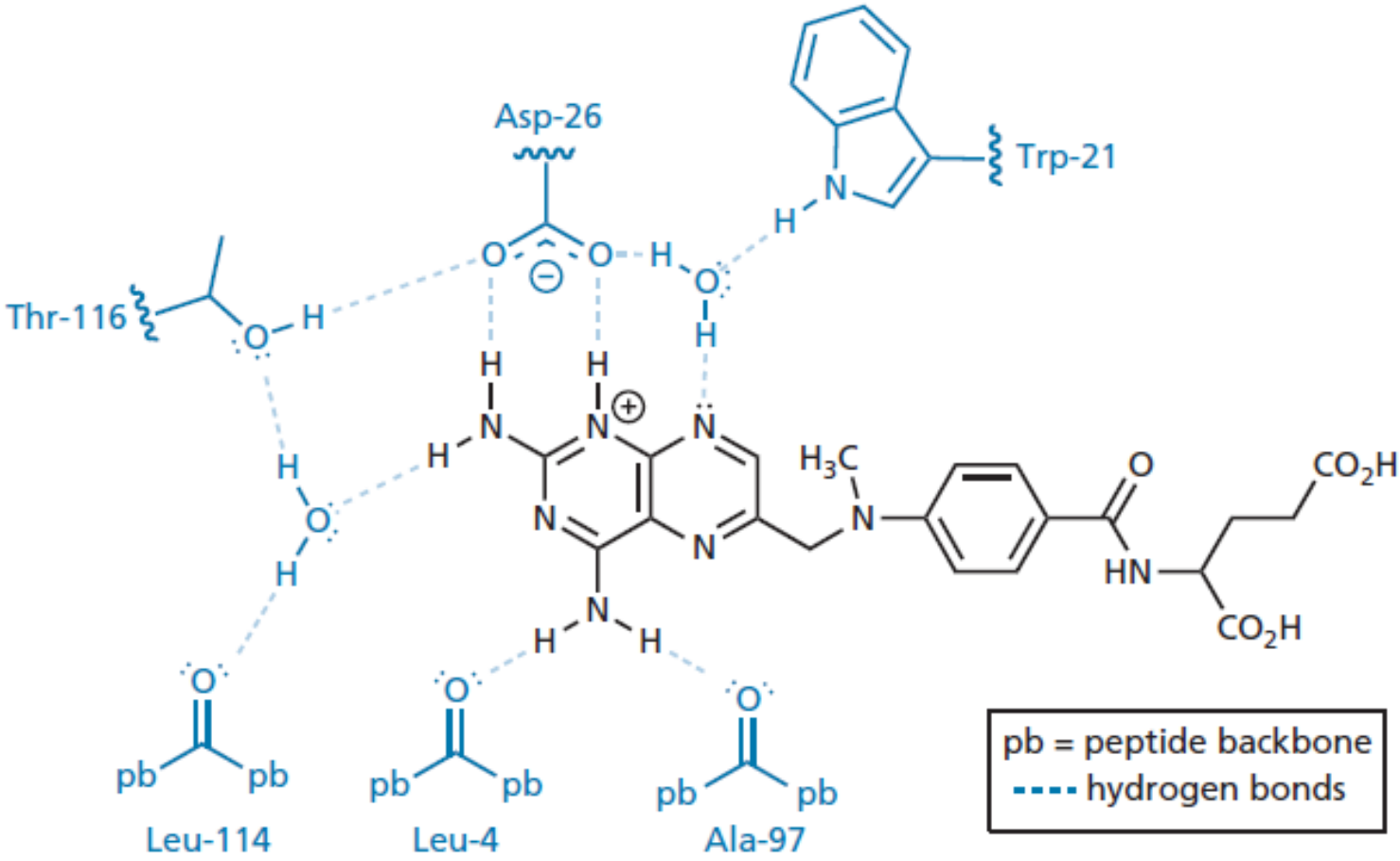
Binding role of Heterocycles

- Van der Waals interactions are also possible to regions of the binding site above and below the plane of the ring system

- Heterocycles can be involved in quite intricate hydrogen bonding networks within a binding site.

For example, the anticancer drug methotrexate contains a diaminopteridine ring system that interacts with its binding site

Binding role of Heterocycles

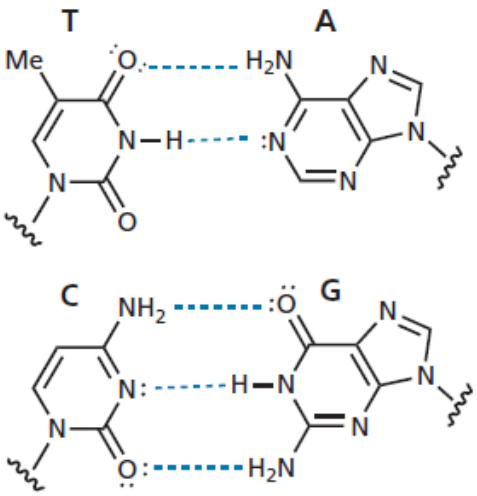


Binding role of Heterocycles

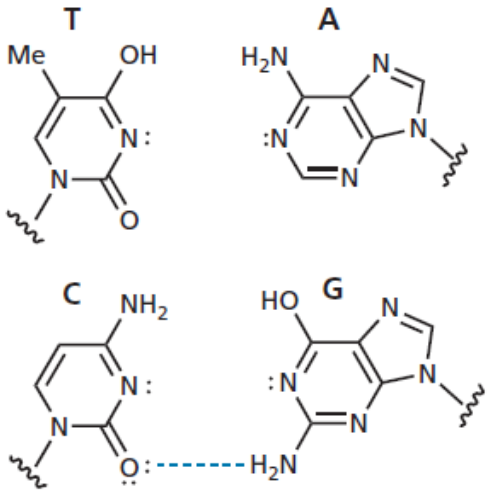
- If the lead compound contains a heterocyclic ring, it is worth synthesizing analogues containing a benzene ring or different heterocyclic rings to explore whether all the heteroatoms present are really necessary.
- A complication with heterocycles is the possibility of tautomers.
- This played an important role in determining the structure of DNA.

Binding role of Heterocycles

- The structure of DNA consists of a double helix with base-pairing between two sets of heterocyclic nucleic acid bases. Base-pairing involves three hydrogen bonds between the base pair guanine and cytosine, and two hydrogen bonds between the base pair adenine and thymine



Correct tautomers for base-pairing



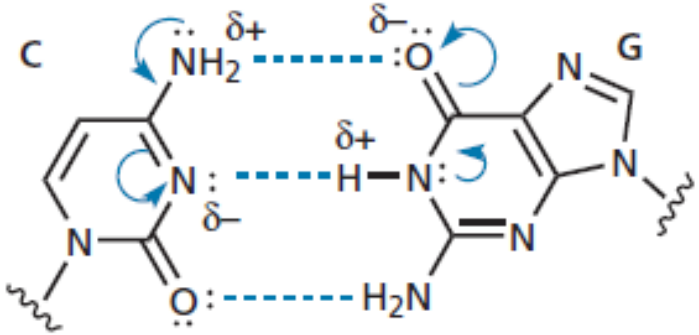
Tautomers resulting in weak base-pairing

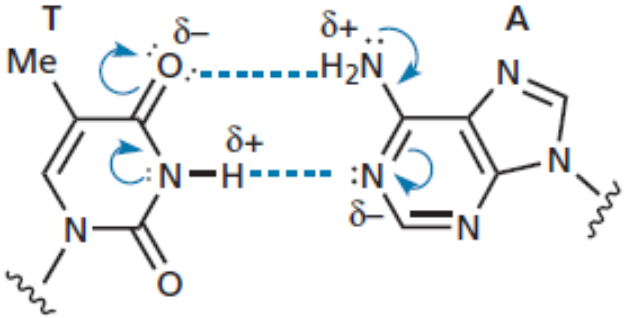
Binding role of Heterocycles

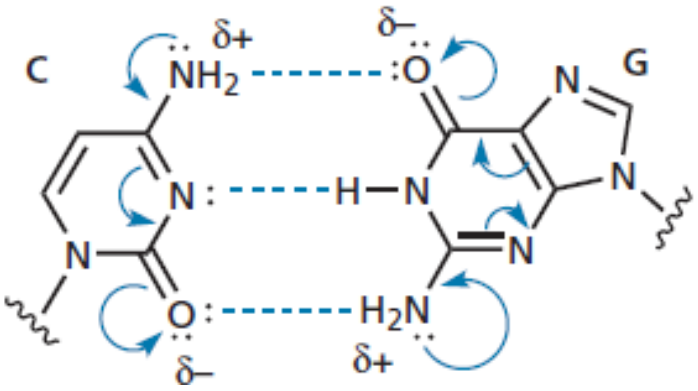
- knowing the preferred tautomers of heterocycles can be important in understanding how drugs interact with their binding sites.
- With heterocyclic compounds, it is possible for a hydrogen bond donor and a hydrogen bond acceptor to be part of a conjugated system.
- Polarization of the electrons in the conjugated system permits π-bond cooperativity, where the strength of the hydrogen bond donor is enhanced by the hydrogen bond acceptor and *vice versa* .
- This has also been called resonance-assisted hydrogen bonding.

Binding role of Heterocycles

- This type of hydrogen bonding is possible for the hydrogen bond donors and acceptors for the nucleic acid base pairs

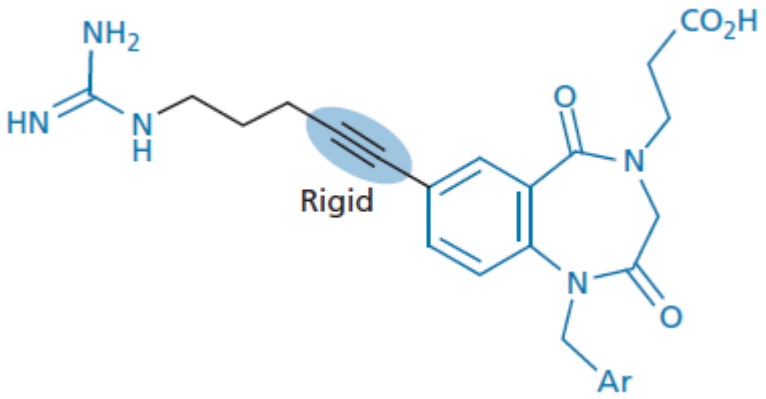






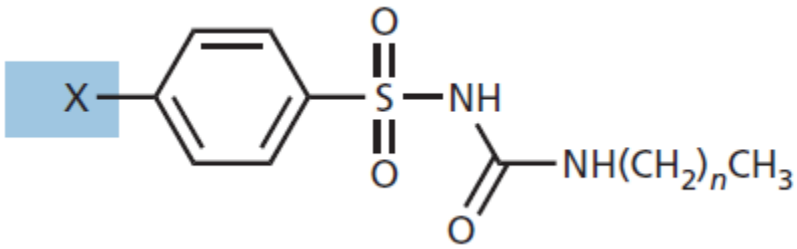
Binding role of other functional groups

- 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).

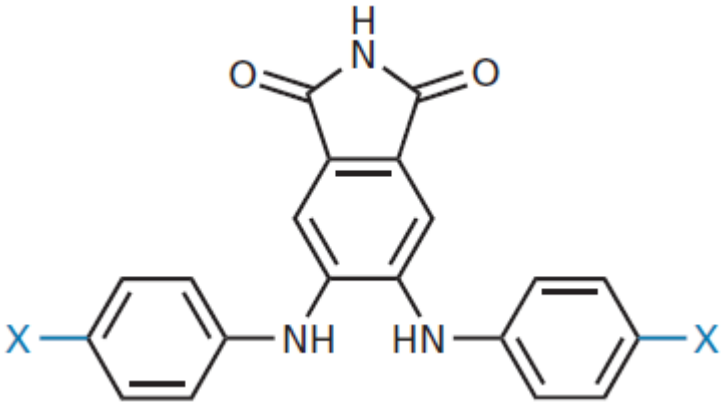


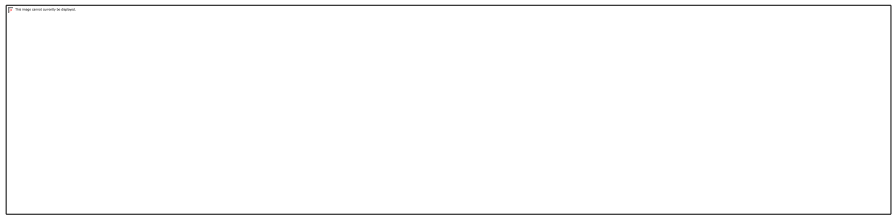
Binding role of other functional groups

- Functional groups may also act as metabolic blockers (e.g. aryl halides).



chlorpropamide (X = Cl; *n* = 2)





Thank You!