Medicinal Chemistry

Optimizing Target Interactions

Dr. Shuaib Alahmad

- strategies that can be used to optimize the interactions of a drug with its target in order to gain better activity and selectivity:

1) Variation of substituents
2) Extension of the structure
3) Chain extension/contraction
4) Ring expansion/contraction
5) Ring variations
6) Ring fusions
7) Isosteres and bioisosteres
8) Simplification of the structure

- strategies that can be used to optimize the interactions of a drug with its target in order to gain better activity and selectivity:

9) Rigidification of the structure
10) Conformational blockers
11) Structure-based drug design and molecular modelling
12) Drug design by NMR spectroscopy
13) Designing drugs to interact with more than one target
14) The elements of luck and inspiration

Variation of substituents

- Varying easily accessible substituents is a common method of fi ne tuning the binding interactions of a drug
- Variation of substituents includes:

I. Variation of Alkyl substituents

II. Variation of Aromatic substituents

III. Synergistic effects

Variation of substituents

I. Variation of Alkyl substituents:

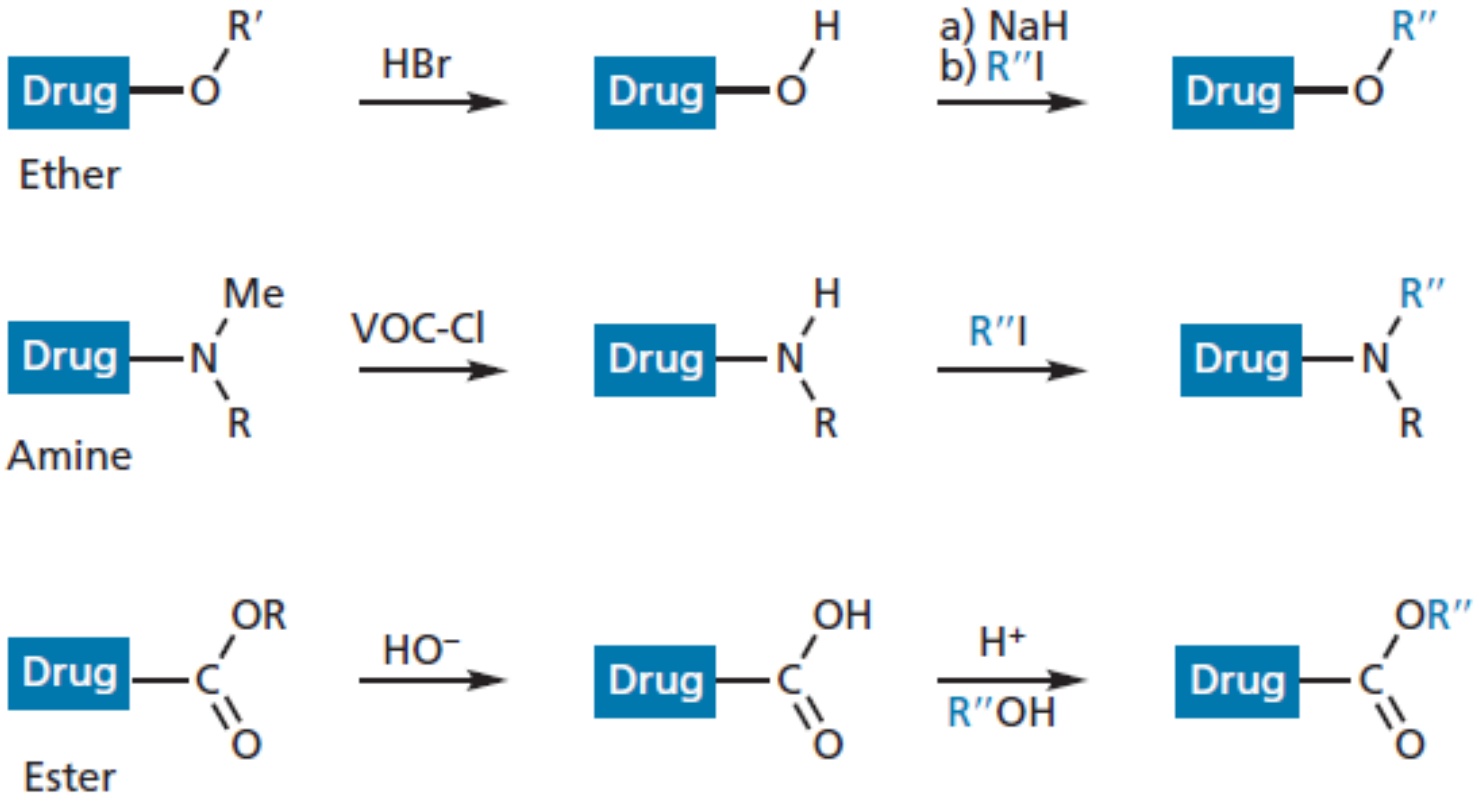
- ✓ Certain alkyl substituents can be varied more easily than others. For example, the alkyl substituents of ethers, amines, esters, and amides are easily varied

- ✓ In these cases, the alkyl substituent already present can be removed and replaced by another substituent.

- ✓ Alkyl substituents which are part of the carbon skeleton of the molecule are not easily removed, and it is usually necessary to carry out a full synthesis in order to vary them.

Variation of substituents

I. Variation of Alkyl substituents:



Variation of substituents

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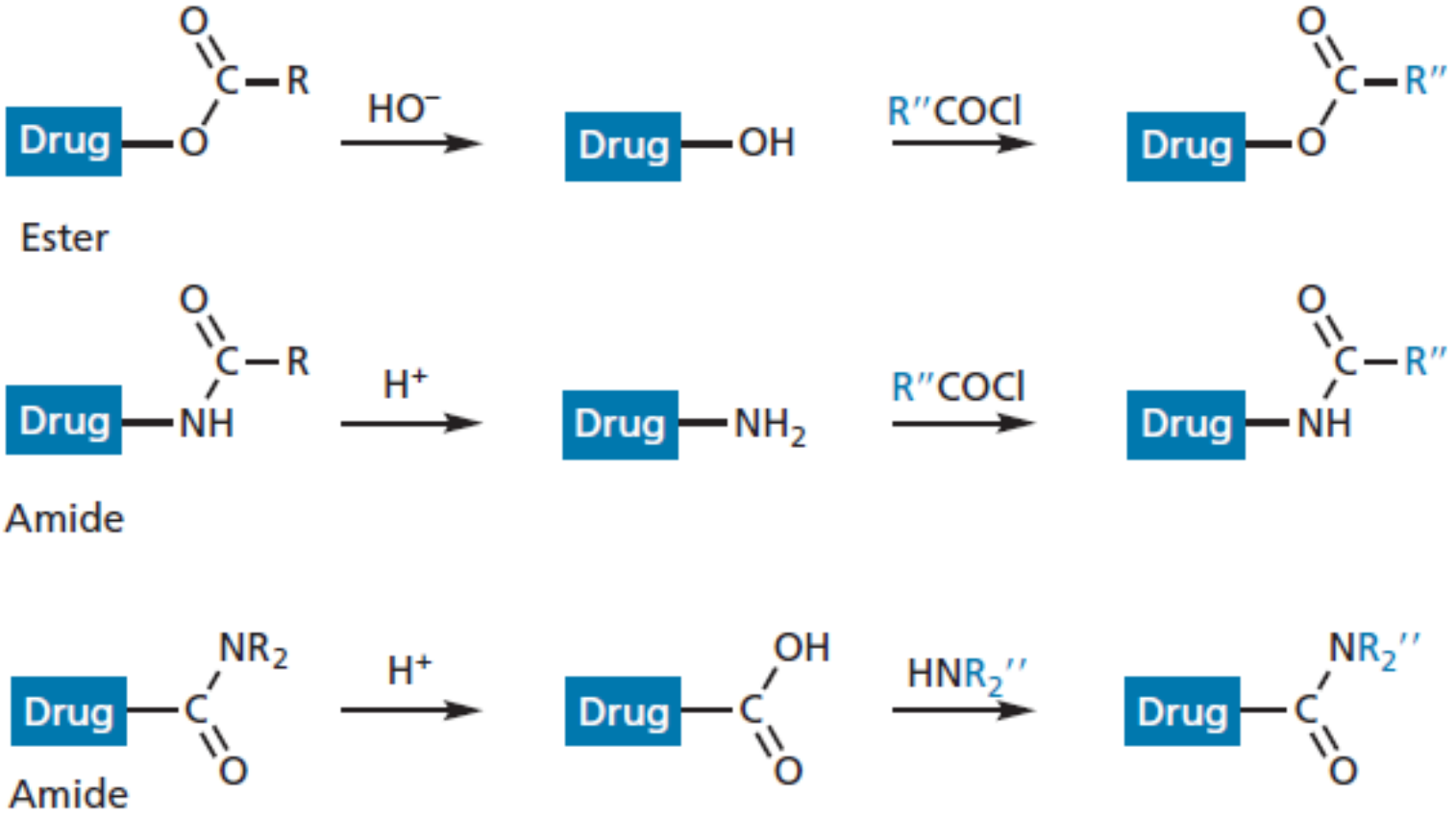

Variation of substituents

I. Variation of Alkyl substituents:

- ✓ If alkyl groups are interacting with a hydrophobic pocket in the binding site, then varying the length and bulk of the alkyl group (e.g. methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or t -butyl) allows one to probe the depth and width of the pocket.

- ✓ Choosing a substituent that will fill the pocket will then increase the binding interaction.
- ✓ Larger alkyl groups may also confer selectivity on the drug.

Variation of substituents

I. Variation of Alkyl substituents:

- ✓ Larger alkyl groups may also confer selectivity on the drug.
- ✓ For example, in the case of a compound that interacts with two different receptors, a bulkier alkyl substituent may prevent the drug from binding to one of those receptors and so cut down side effects.
- ✓ For example, isoprenaline 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

Variation of substituents

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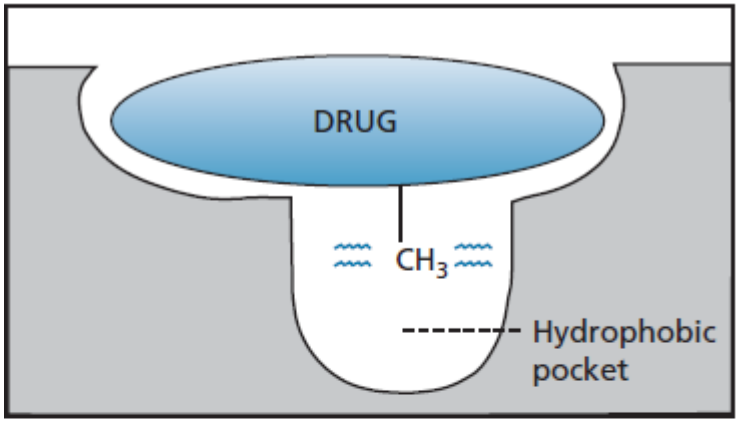
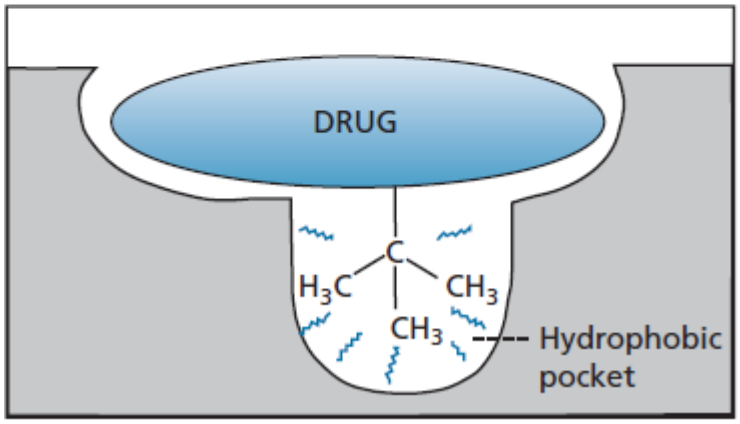
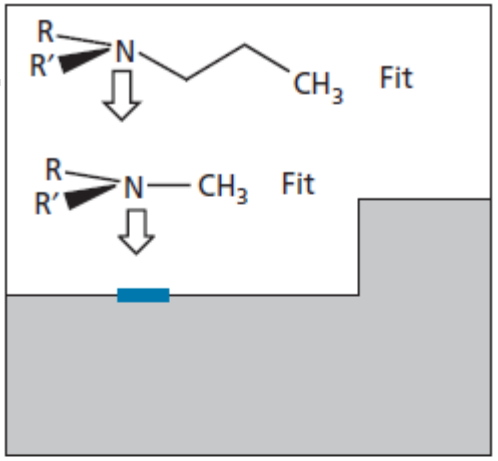
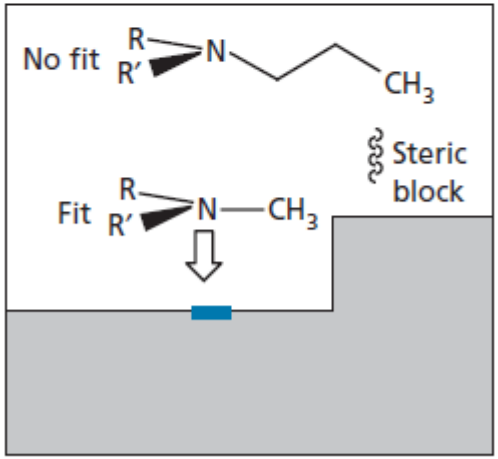




van der Waals interactions



Receptor 1



Receptor 2

Binding region for N

Variation of substituents

II. Variation of Aromatic substituents:

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

- ✓ For example, the best anti-arrythmic activity for a series of benzopyrans was found when the sulphonamide substituent was at position 7 of the aromatic ring

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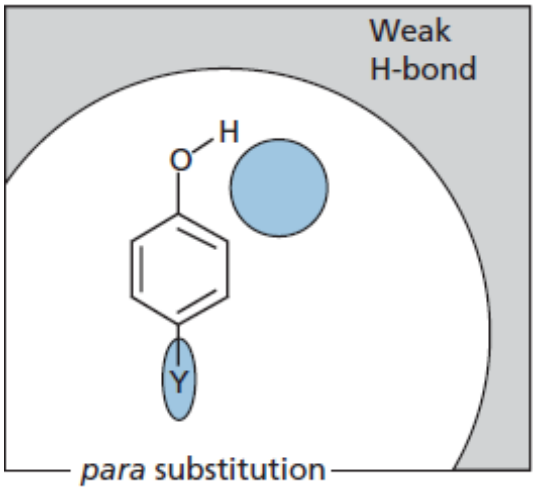

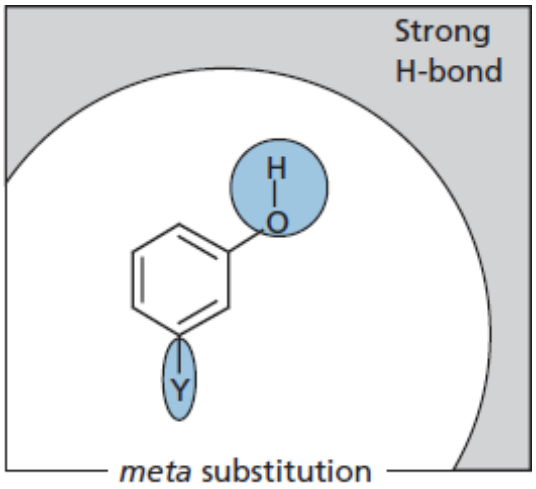

Variation of substituents

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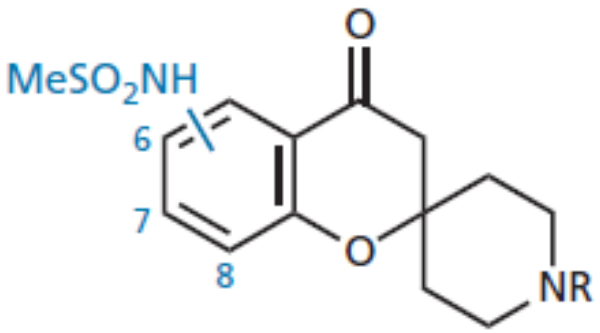


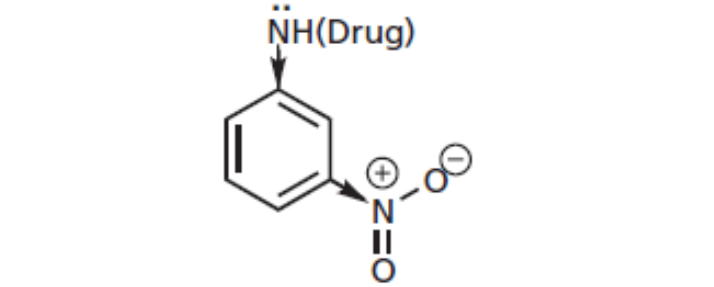
Variation of substituents

II. Variation of Aromatic substituents:

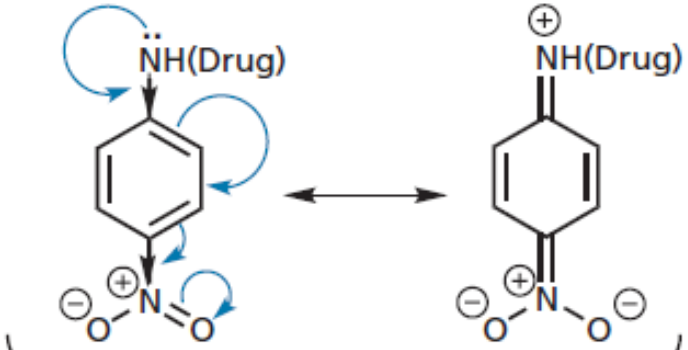
- ✓ Changing the position of one substituent may have an important effect on another.
- ✓ For example, an electron withdrawing nitro group will affect the basicity of an aromatic amine more significantly if it is at the *para* position rather than the *meta* position.
- ✓ At the *para* position, the nitro group will make the amine a weaker base and less liable to protonate.
- ✓ This would decrease the amine's ability to interact with ionic binding groups in the binding site, and decrease activity.

Variation of substituents

II. Variation of Aromatic substituents:



meta (inductive electron-withdrawing effect)



para (electron-withdrawing effect due to resonance *and* inductive effects)

Variation of substituents

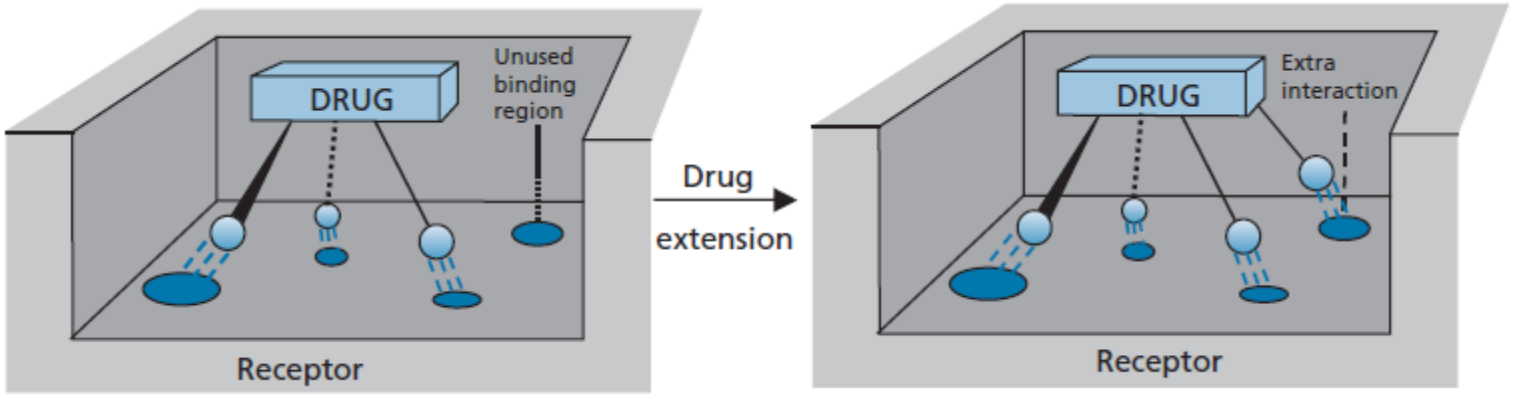
III. Synergistic effects

- ✓ When varying substituents, it is normal to study analogues where only one substituent is added or altered at a time. In that way, one can identify those substituents that are good for activity and those that are not.
- ✓ However, it does not take into account the synergistic effect that two or more substituents may have on activity.
- ✓ For example, two substituents that are individually bad for activity may actually be beneficial for activity when they are both present.
- ✓ The design of the anticancer drug Sorafenib provides an illustration of this effect

Extension of the structure

- The strategy of extension involves the addition of another functional group or substituent to the lead compound in order to probe for extra binding interactions with the target.
- Lead compounds are capable of fitting the binding site and have the necessary functional groups to interact with some of the important binding regions present.
- However, it is possible that they do not interact with all the binding regions available. For example, a lead compound may bind to three binding regions in the binding site but fail to use a fourth.
- Therefore, why not add extra functional groups to probe for that fourth region?

Extension of the structure

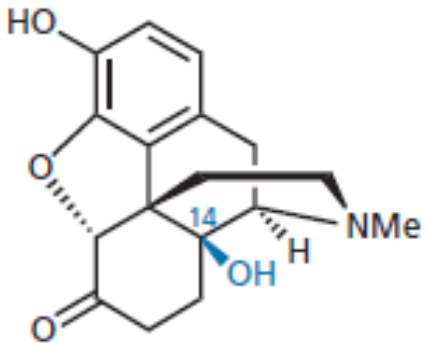


Extension of the structure

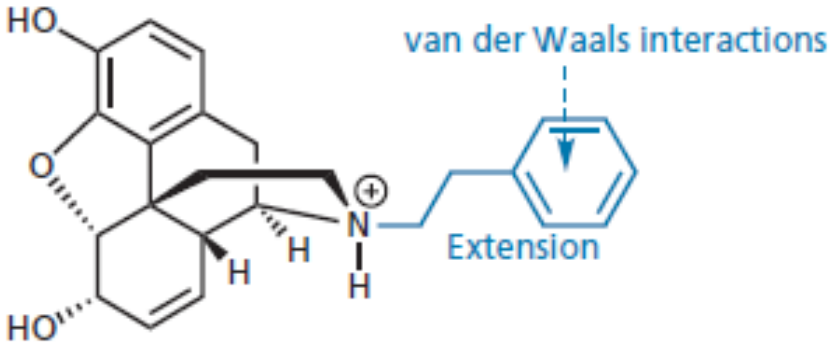
- Extension tactics are often used to find extra hydrophobic regions in a binding site by adding various alkyl or arylalkyl groups.
- These groups can be added to functional groups, such as alcohols, phenols, amines, and carboxylic acids should they be present in the drug, as long as this does not disrupt important binding interactions that are already present.
- Alternatively, they could be built into the building blocks used in the synthesis of various analogues.
- By the same token, substituents containing polar functional groups could be added to probe for extra hydrogen bonding or ionic interactions.

Extension of the structure

- The extension tactic has been used successfully to produce more active analogues of morphine



Oxymorphone
(2.5 × activity of morphine)



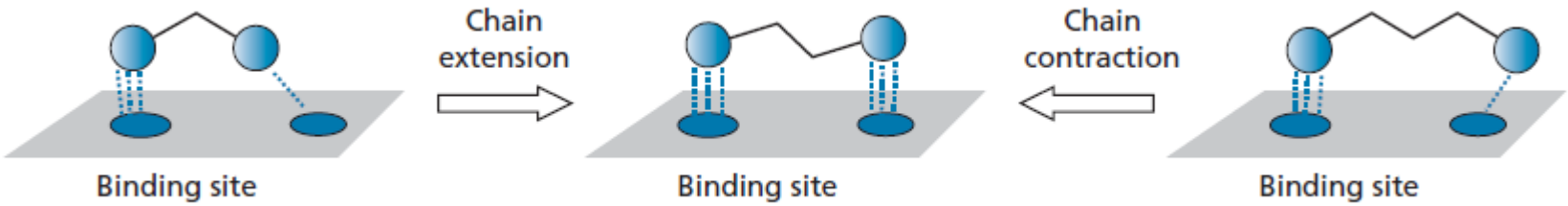
N-Phenethylmorphine
(14 × activity of morphine)

Extension of the structure

- Extension strategies are used to strengthen the binding interactions and activity of a receptor agonist or an enzyme inhibitor, but
- Extension strategies can also be used to convert an agonist into an antagonist.
- This will happen if the extra binding interaction results in a different induced fit from that required to activate the receptor. As a result, the antagonist binds to an inactive conformation of the receptor and blocks access to the endogenous agonist.
- The strategy has also been used to alter an enzyme substrate into an inhibitor

Chain extension/contraction

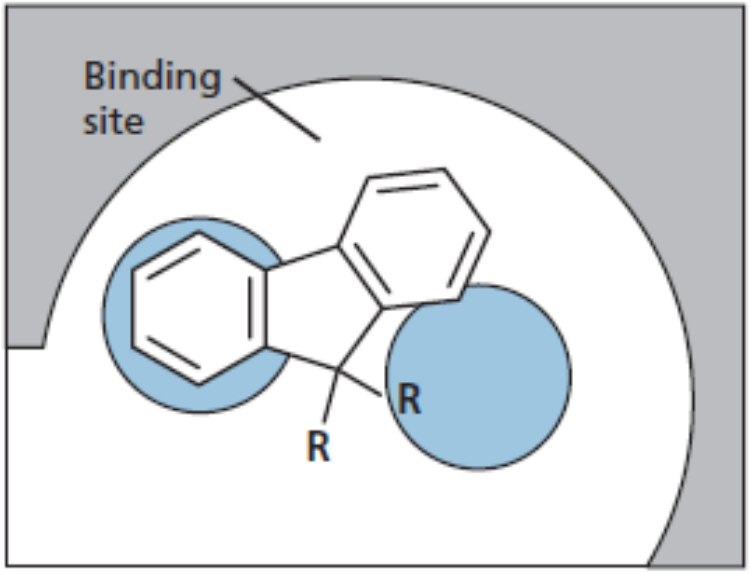
- ✓ Some drugs have two important binding groups linked together by a chain, in which case it is possible that the chain length is not ideal for the best interaction.
- ✓ Therefore, shortening or lengthening the chain length is a useful tactic to try



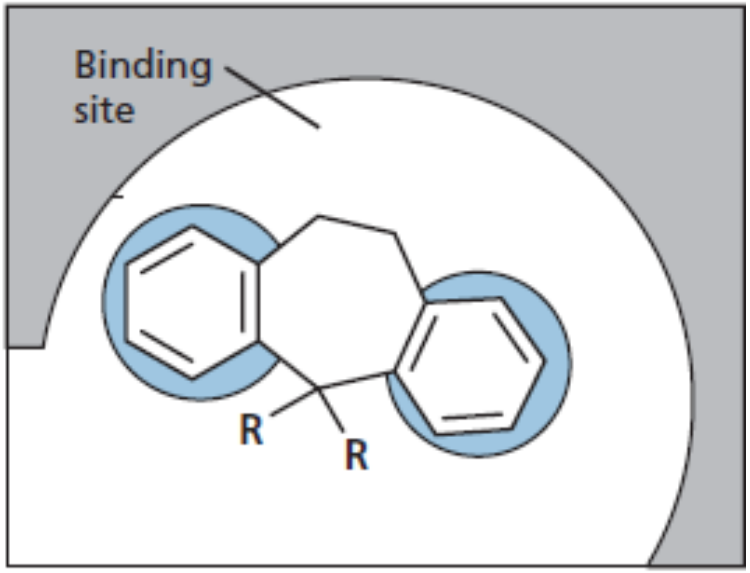
Ring expansion/contraction

- If a drug has one or more rings that are important to binding, it is generally worth synthesizing analogues where one of these rings is expanded or contracted.
- The principle behind this approach is much the same as varying the substitution pattern of an aromatic ring.
- Expanding or contracting a ring may put other rings in different positions relative to each other, and may lead to better interactions with specific regions in the binding site.
- Varying the size of a ring can also bring substituents into a good position for binding.

Ring expansion/contraction



6,5,6 ring system has a poor interaction with both hydrophobic regions



6,7,6 ring system has the optimum interaction with both hydrophobic regions

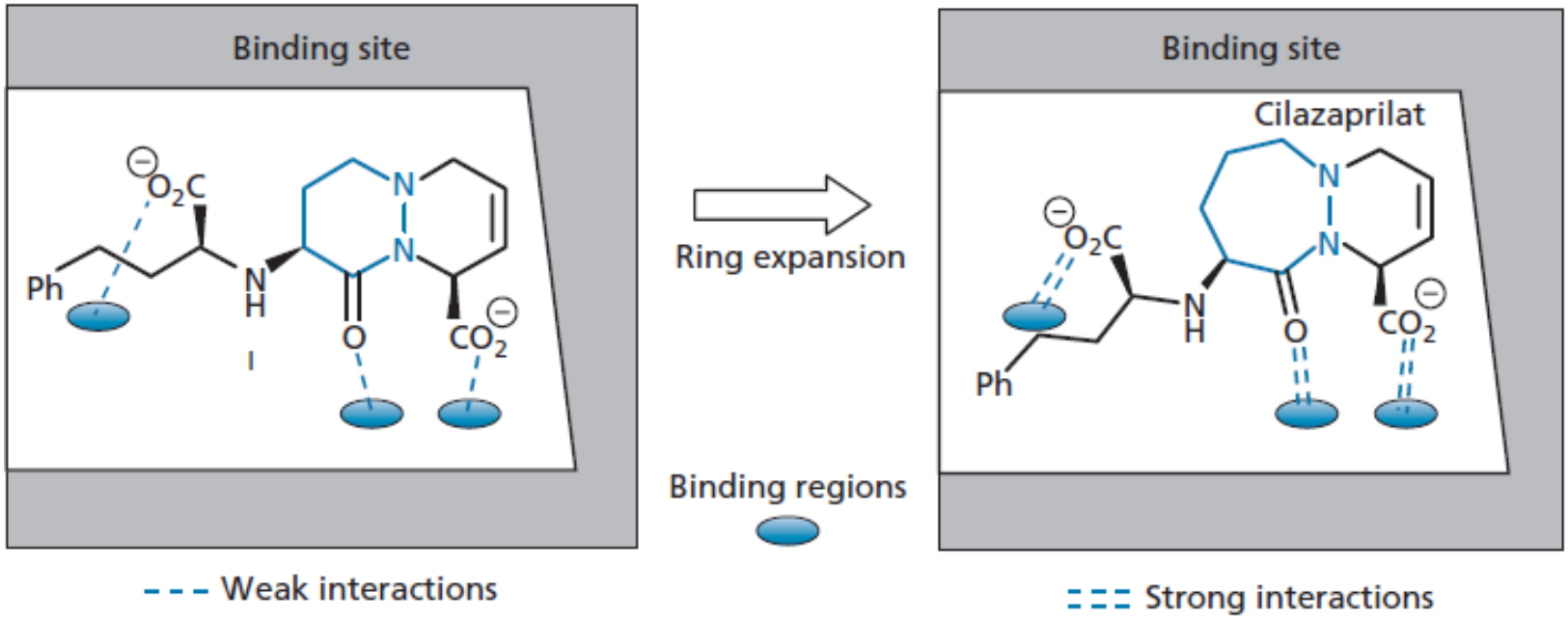
Ring expansion/contraction

- For example, during the development of the anti-hypertensive agent Cilazaprilat (another ACE inhibitor), the bicyclic structure I showed promising activity.

- The important binding groups were the two carboxylate groups and the amide group.

- By carrying out various ring contractions and expansions , Cilazaprilat was identified as the structure having the best interaction with the binding site.

Ring expansion/contraction

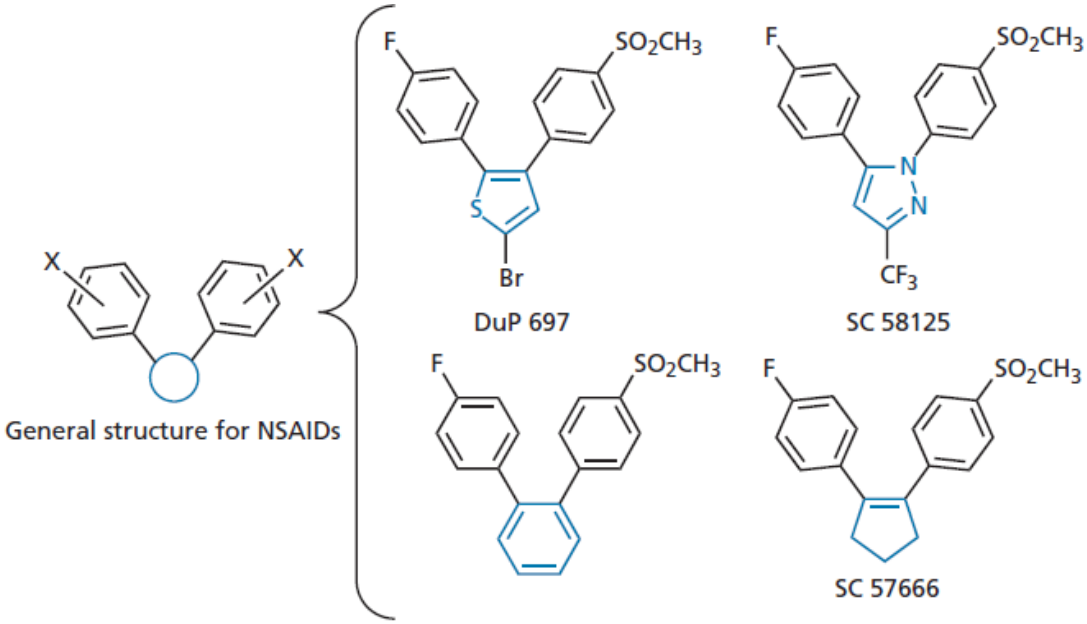


Ring variations

- 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 ring size and heteroatom positions.

- For example, several non-steroidal anti-inflammatory agents (NSAIDs) have been reported, all consisting of a central ring with 1,2-biaryl substitution.
- Different pharmaceutical companies have varied the central ring to produce a range of active compounds

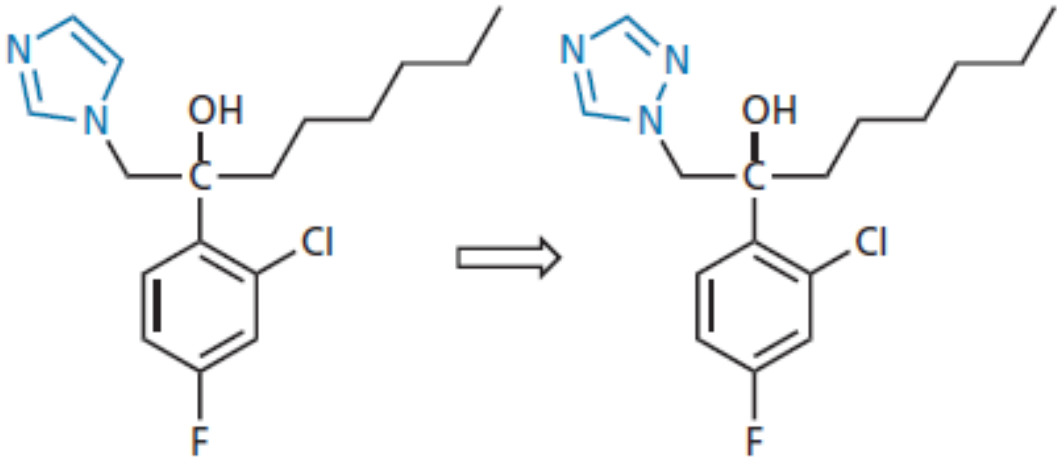
Ring variations



- ✓ A lot of these changes are merely ways of avoiding patent restrictions (me too drugs), but there can often be significant improvements in activity, as well as increased selectivity and reduced side effects (me-better drugs).

Ring variations

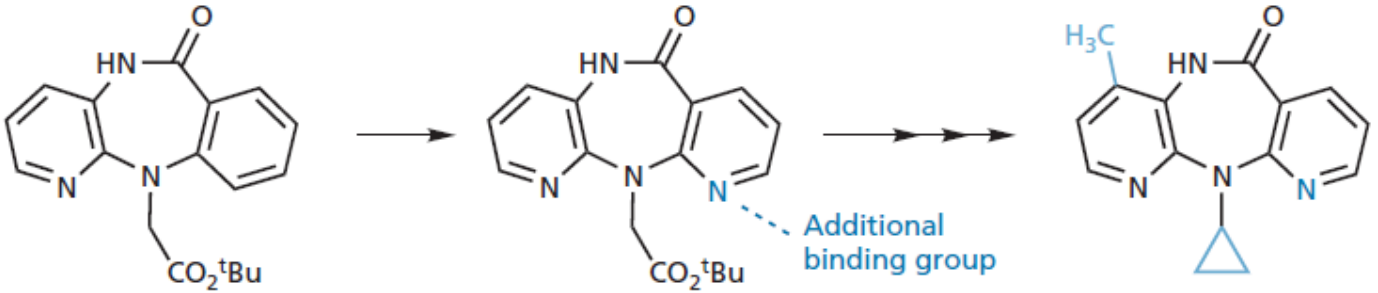
- For example, the antifungal agent (I) acts against an enzyme present in both fungal and human cells.
- Replacing the imidazole ring of structure (I) with a 1,2,4-triazole ring to give UK 46245 resulted in better selectivity against the fungal form of the enzyme.



Structure I UK 46245

Ring variations

- ✓ One advantage of altering an aromatic ring to a hetero aromatic ring is that it introduces the possibility of an extra hydrogen bonding interaction with the binding site, should a suitable binding region be available (*extension strategy*).
- ✓ For example, structure I was the lead compound for a project looking into novel antiviral agents.
- ✓ Replacing the aromatic ring with a pyridine ring resulted in an additional binding interaction with the target enzyme.



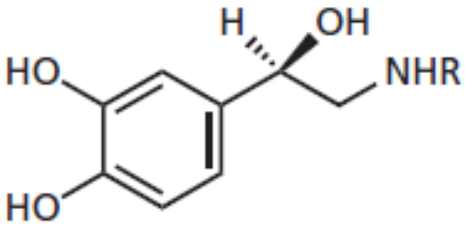
Lead compound (I) Nevirapine

Ring fusions

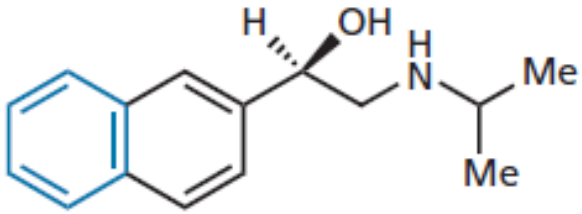
- Extending a ring by ring fusion can sometimes result in increased interactions or increased selectivity.

- One of the major advances in the development of the selective β-blockers was the replacement of the aromatic ring in adrenaline with a naphthalene ring system (pronethalol).
- This resulted in a compound that was able to distinguish between two very similar receptors (the α- and β-receptors for adrenaline).

Ring fusions



R = Me Adrenaline
R = H Noradrenaline



Pronethalol

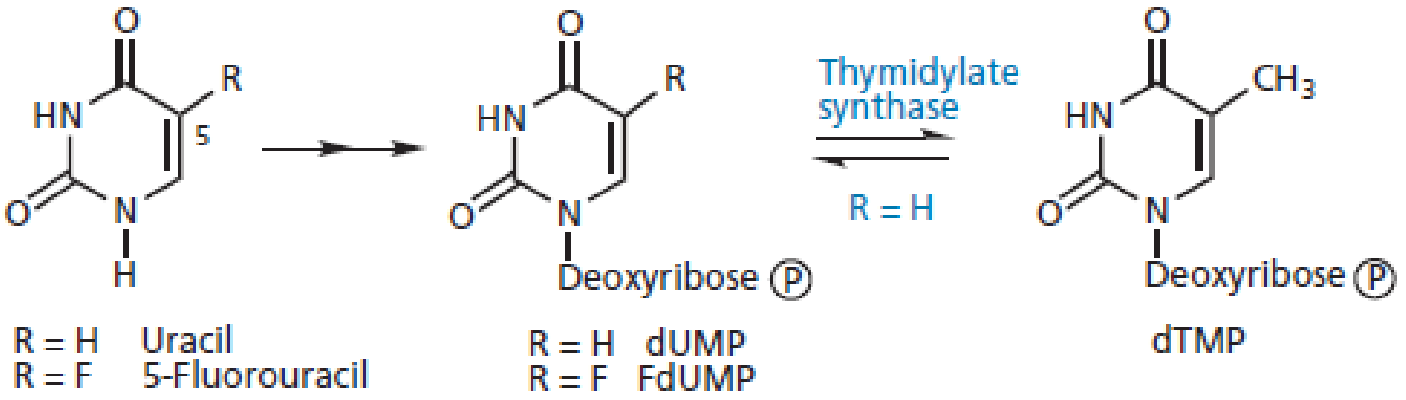
- ✓ One possible explanation for this could be that the β-receptor has a larger van der Waals binding area for the aromatic system than the α-receptor, and can interact more strongly with pronethalol than with adrenaline.
- ✓ Another possible explanation is that the naphthalene ring system is sterically too big for the α-receptor, but is just right for the β-receptor.

Isosteres and bioisosteres

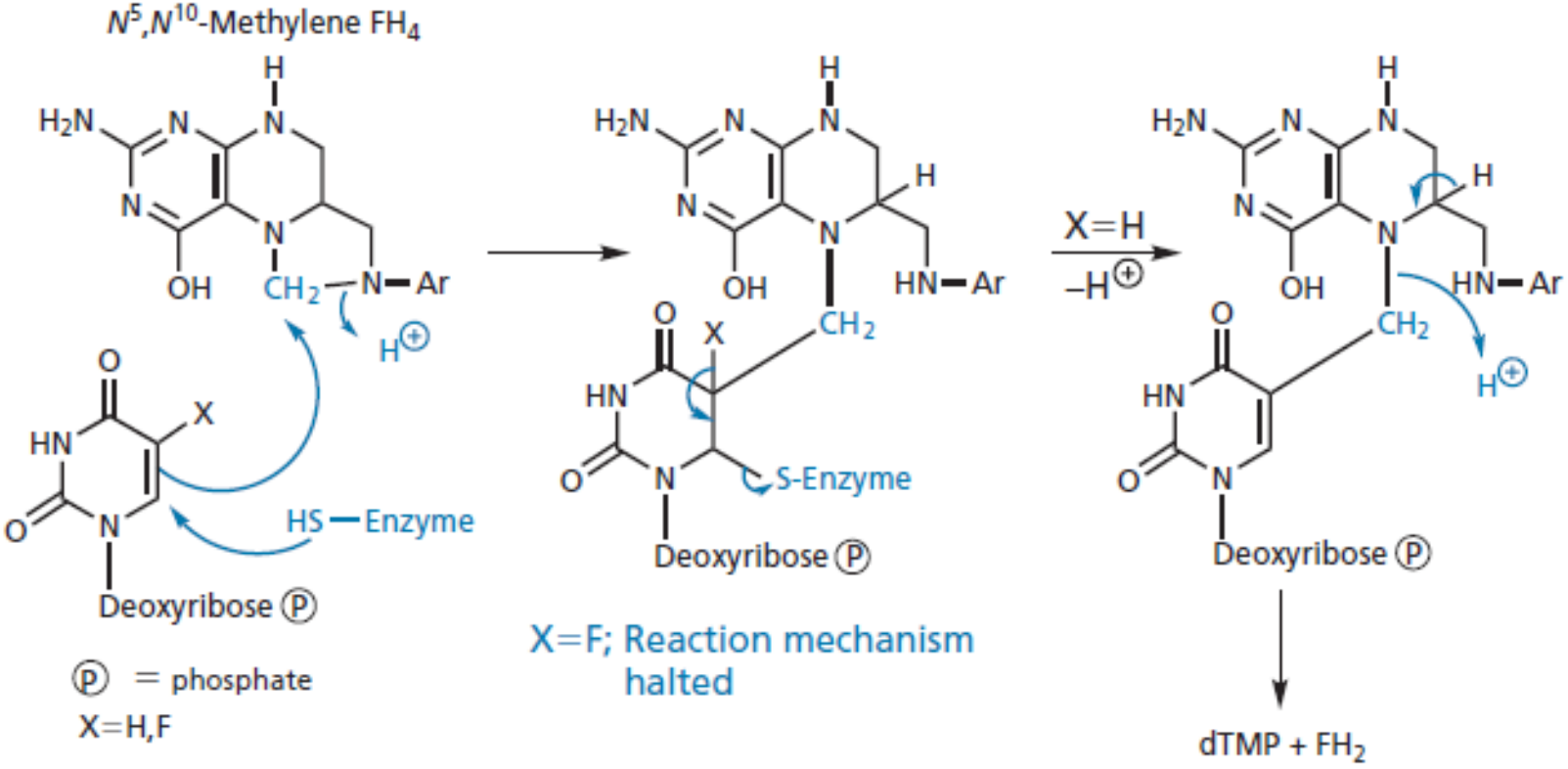
- ✓ Isosteres have often been used in drug design to vary the character of the molecule in a rational way with respect to features such as size, polarity, electronic distribution, and bonding.
- ✓ Some isosteres can be used to determine the importance of size towards activity, whereas others can be used to determine the importance of electronic factors. For example, fluorine is often used as an isostere of hydrogen as 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.

Isosteres and bioisosteres

- ✓ 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 thymidylate synthase because it appears little different from the normal substrate uracil.

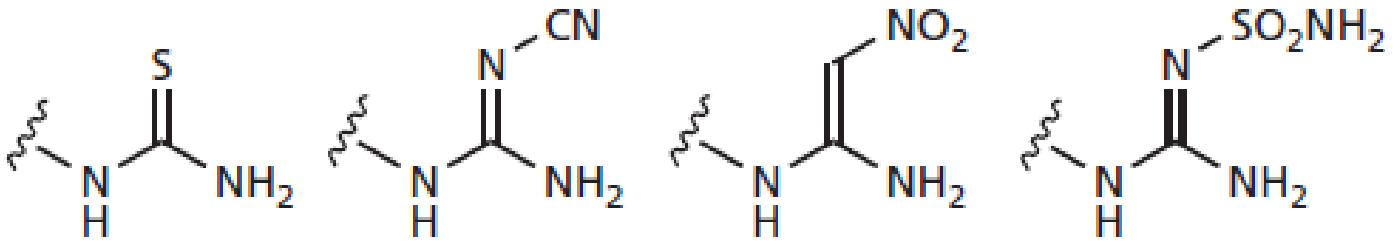


Isosteres and bioisosteres



Isosteres and bioisosteres

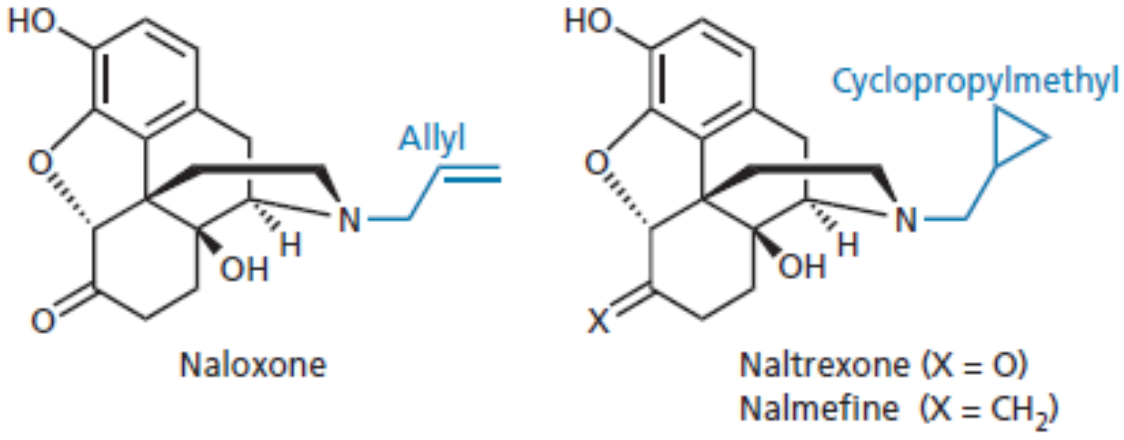
- ✓ Several non-classical isosteres have been used in drug design as replacements for particular functional groups.
- ✓ Non-classical isosteres are groups that do not obey the steric and electronic rules used to define classical isosteres, but which have similar physical and chemical properties.
- ✓ For example, the structures shown below in are non-classical isosteres for a thiourea group.
- ✓ They are all planar groups of similar size and basicity.



Thiourea

Isosteres and bioisosteres

- ✓ The term bioisostere is used in drug design and includes both classical and non-classical isosteres.
- ✓ A bioisostere is a group that can be used to replace another group while retaining the desired biological activity.
- ✓ For example, a cyclopropyl group has been used as a bioisostere for an alkene group in opioid antagonists.



Isosteres and bioisosteres

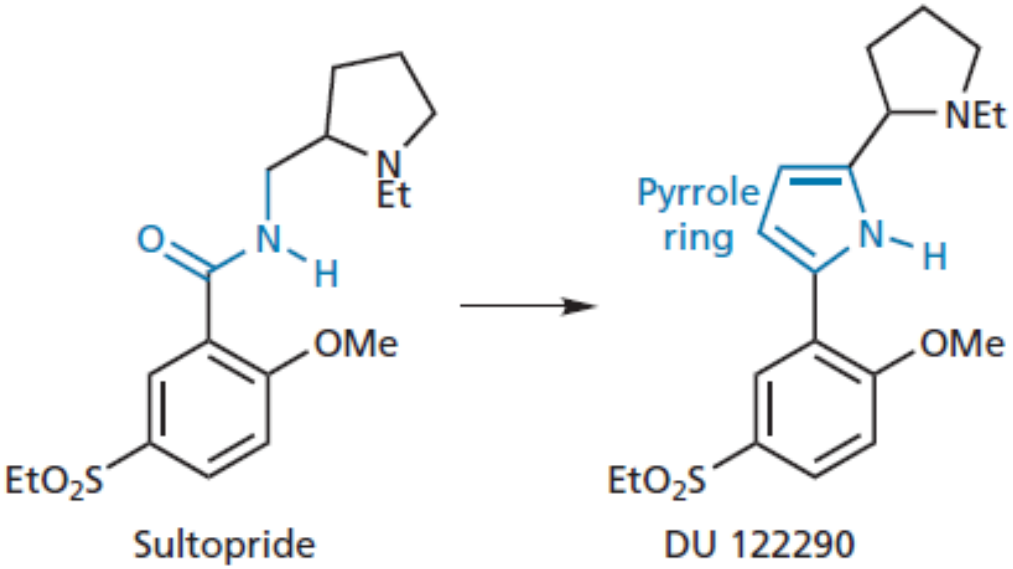
- ✓ Bioisosteres are often used to replace a functional group that is important for target binding, but is problematic in one way or another.
- ✓ For example, the thiourea group was present as an important binding group in early histamine antagonists, but was responsible for toxic side effects.
- ✓ Replacing it with bioisosteres allowed the important binding interactions to be retained for histamine antagonism but avoided the toxicity problems

Isosteres and bioisosteres

- As stated above, bioisosteres are commonly used in drug design to replace a problematic group while retaining activity.
- In some situations, the use of a bioisostere can actually increase target interactions and/or selectivity.
- For example, a pyrrole ring has frequently been used as a bioisostere for an amide.

Isosteres and bioisosteres

- ✓ Carrying out this replacement on the dopamine antagonist sultopride led to increased activity and selectivity towards the dopamine D3 receptor over the dopamine D2 receptor.
- ✓ Such agents show promise as antipsychotic agents that lack the side effects associated with the D 2 -receptor.



Isosteres and Bioisosteres

- Introducing a bioisostere to replace a problematic group often involves introducing further functional groups that might form extra binding interactions with the target binding site (*Extension*).
- For example, a 10-fold increase in activity was observed for an antiviral agent when an *N*-acylsulphonamide was used as a bioisostere for a carboxylic acid.
- The *N*-acylsulphonamide group introduces the possibility of further hydrogen bonding or van der Waals interactions with the binding site.

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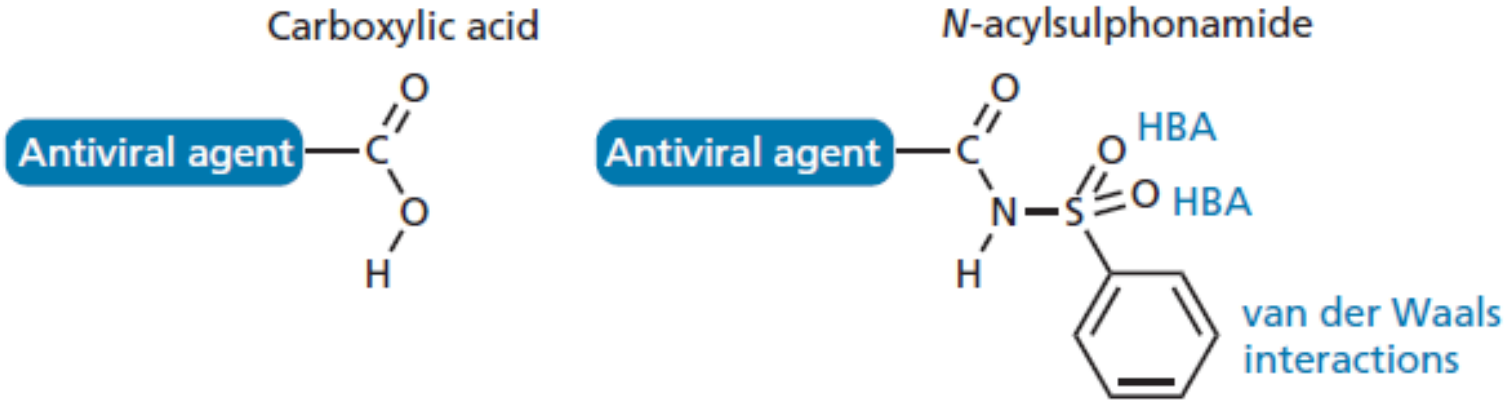

Simplification of the structure

- ✓ Simplification is a strategy which is commonly used on the often complex lead compounds arising from natural sources.

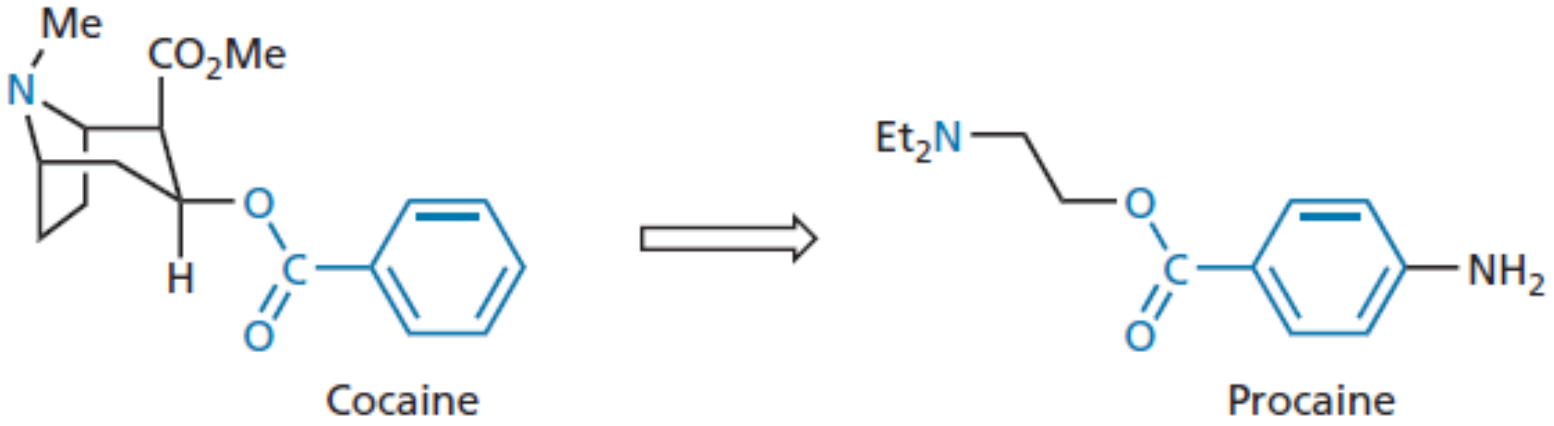

FIGURE 1 Simplification of cocaine (pharmacophore shown in colour).

Simplification of the structure

- ✓ 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

1. removing functional groups which are not part of the pharmacophore,
2. simplifying the carbon skeleton (for example removing rings)
3. removing asymmetric centers

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2. simplifying the carbon skeleton (for example removing rings)
3. removing asymmetric centers

Simplification of the structure

- ✓ Various tactics can be used to remove asymmetric carbon centers:

1. replacing the carbon center with nitrogen has been effective in many cases.
2. introducing symmetry where originally there was none.

Simplification of the structure

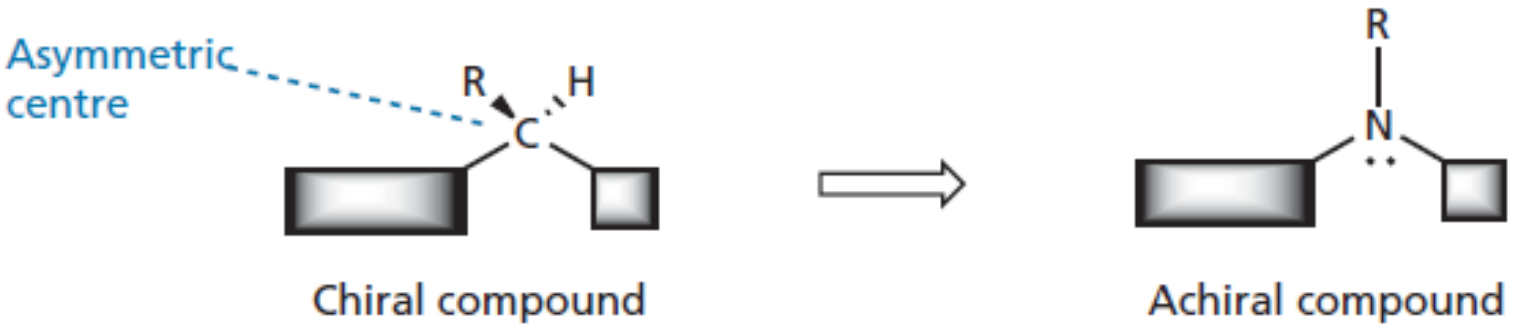


FIGURE 13.52 Replacing an asymmetric carbon with nitrogen.

Simplification of the structure

1. replacing the carbon centre with nitrogen has been effective in many cases.

✓ An illustration of this can be seen in the design of thymidylate synthase inhibitors

Simplification of the structure

- ✓ Various tactics can be used to remove asymmetric carbon centers:

2. Another tactic is to introduce symmetry where originally there was none. For example, the muscarinic agonist (II) was developed from (I) in order to remove asymmetry. Both structures have the same activity.

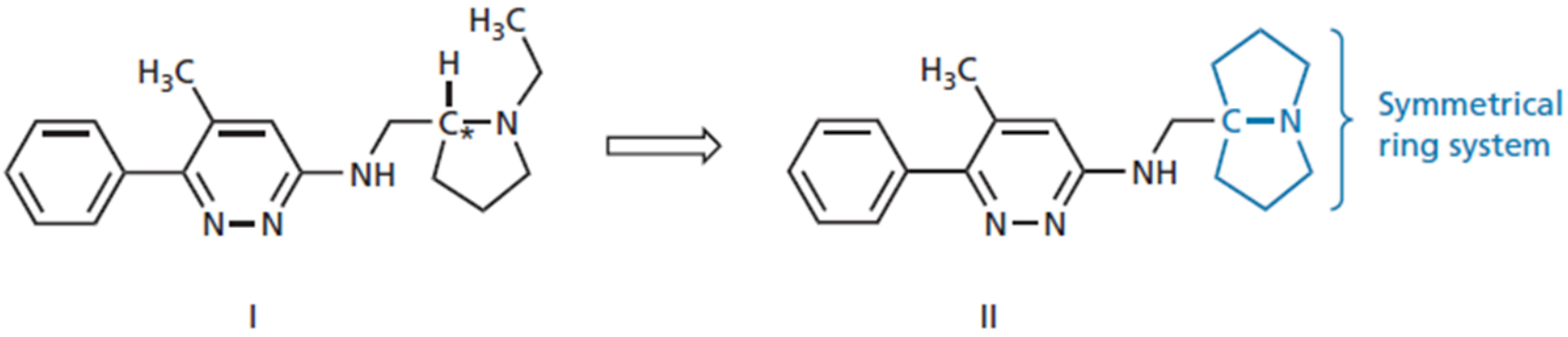


FIGURE 13.53 Introducing symmetry.

Rigidification of the structure

- ✓ The strategy of rigidification is to make the molecule more rigid, such that the active conformation is retained and the number of other possible conformations is decreased.
- ✓ Rigidification has often been used to increase the activity of a drug or to reduce its side effects.

- ✓ Rigidification strategy should reduce the possibility of other receptor interactions and side effects.
- ✓ Rigidification strategy should also increase activity. by making the drug more rigid, it is more likely to be in the active conformation when it approaches the target binding site and should bind more readily.

Rigidification of the structure

- ✓ Incorporating the skeleton of a flexible drug into a ring is the usual way of locking a conformation

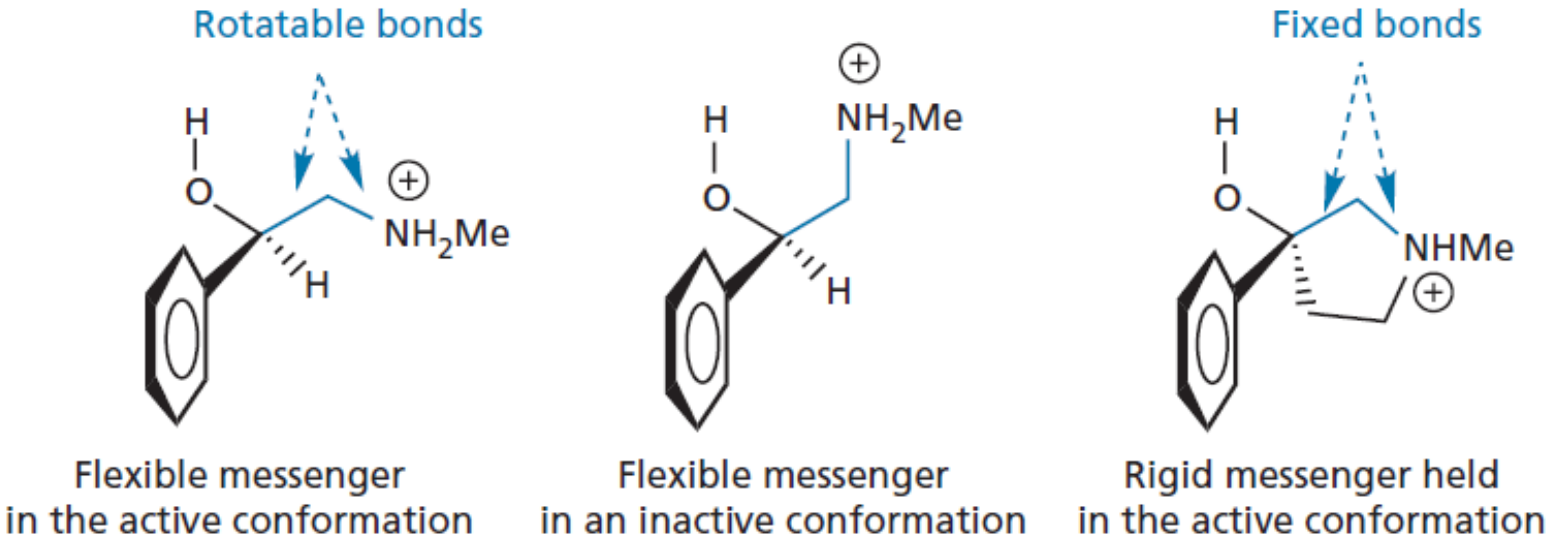
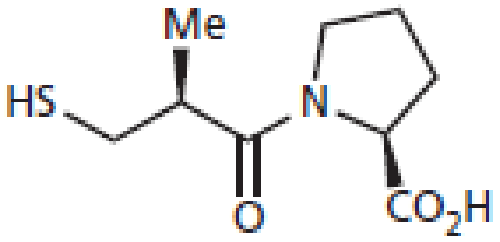


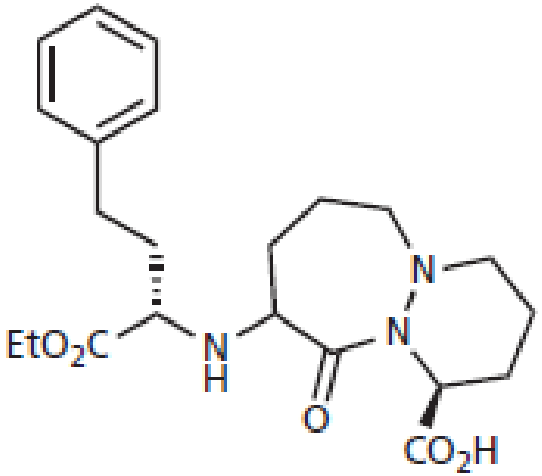
FIGURE 13.55 Rigidification of a molecule by locking rotatable bonds within a ring.

Rigidification of the structure

- Similar rigidification tactics have been useful in the development of the anti-hypertensive agent cilazapril from captopril



Captopril



Cilazapril
(Hoffmann-LaRoche)

Rigidification of the structure

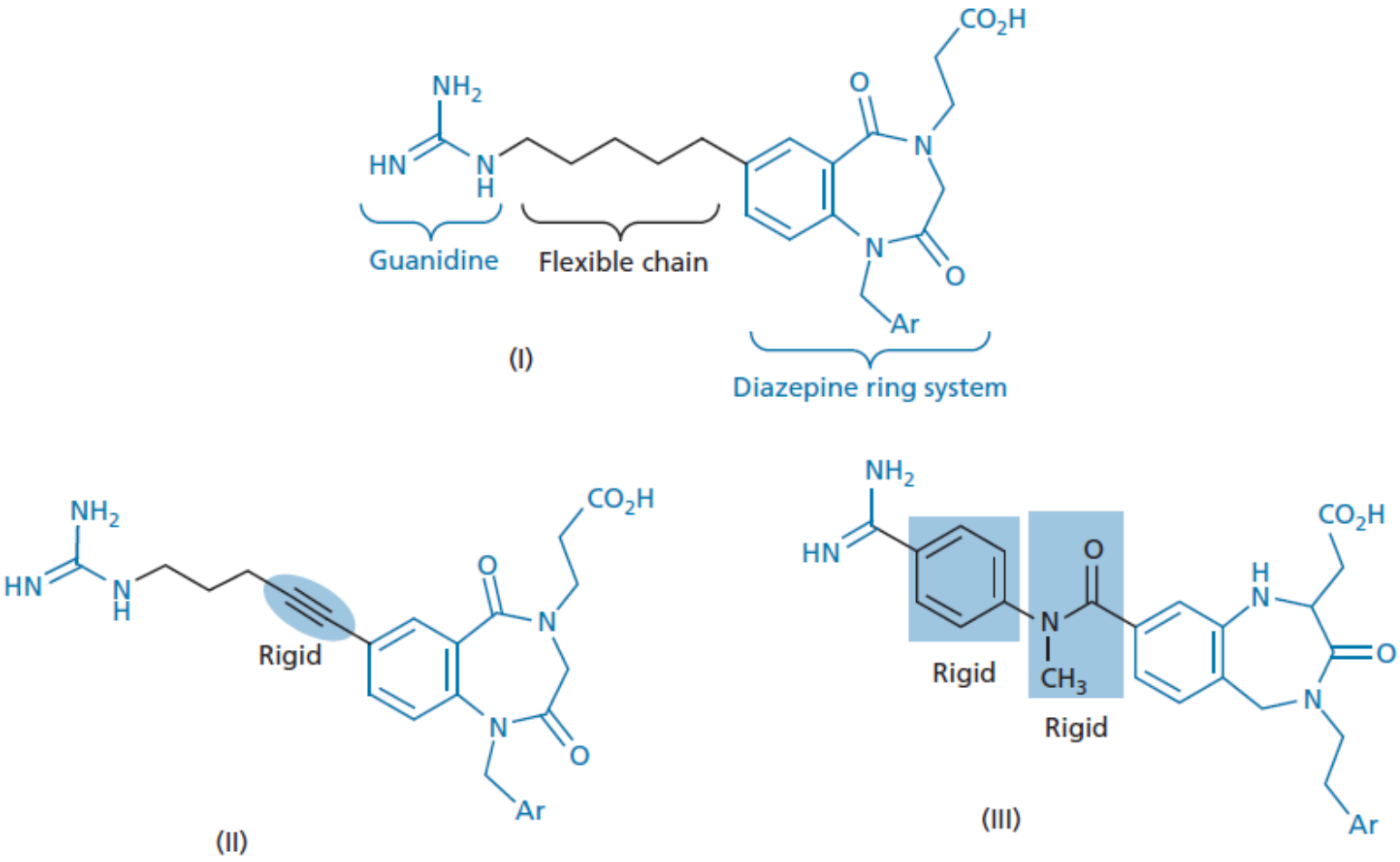
- ✓ Locking a rotatable bond into a ring is not the only way a structure can be rigidified.
- ✓ A flexible side chain can be partially rigidified by incorporating a rigid functional group such as a :

1) double bond
2) alkyne
3) amide
4) aromatic ring

Rigidification of the structure

- Rigidification also has potential disadvantages:
- Rigidified structures may be more complicated to synthesize.
- There is also no guarantee that rigidification will retain the active conformation; it is perfectly possible that rigidification will lock the compound into an inactive conformation.
- Another disadvantage involves drugs acting on targets which are prone to mutation. If a mutation alters the shape of the binding site, then the drug may no longer be able to bind, whereas a more flxible drug may adopt a different conformation that *could* bind.

Rigidification of the structure



Rigidification of flexible chains.