OPTIMIZING TARGET INTERACTIONS

4. DRUG DESIGN - OPTIMISING BINDING INTERACTIONS

AIM - To optimise binding interactions with target

REASONS

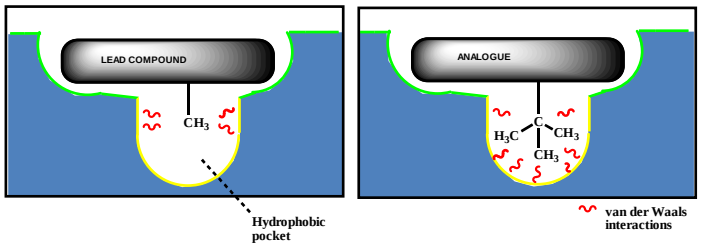
- To increase activity and reduce dose levels
- To increase selectivity and reduce side effects

STRATEGIES

- Vary alkyl substituents
- Vary aryl substituents
- Extension
- Chain extensions / contractions
- Ring expansions / contractions
- Ring variation
- Isosteres
- Simplification
- Rigidification

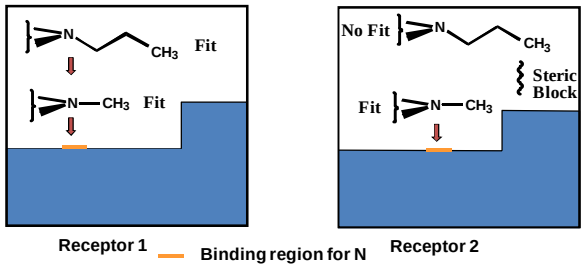
4.1 Vary Alkyl Substituents

- alkyl group may interact with hydrophobic region in binding site
- vary length and bulk of group to optimise interaction

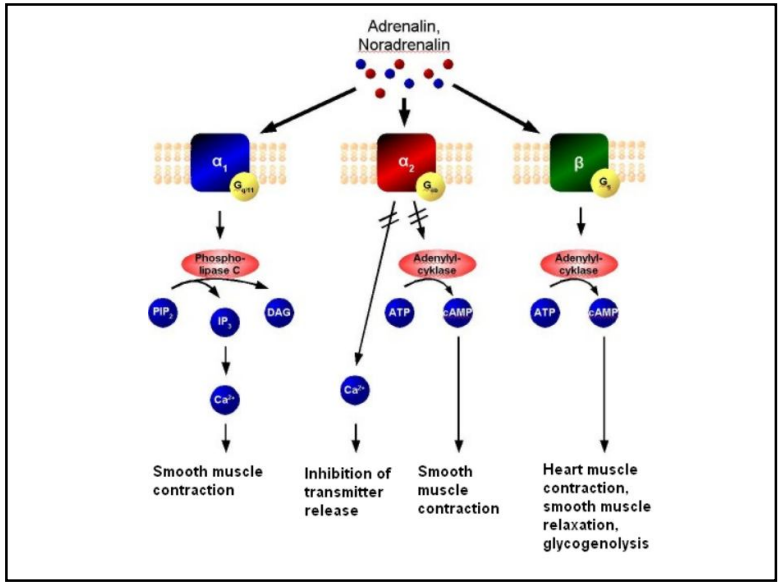


4.1 Vary Alkyl Substituents

vary length and bulk of alkyl group to introduce selectivity

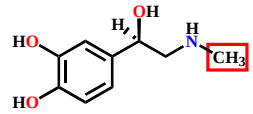


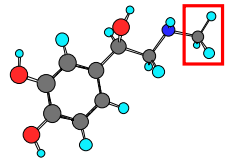
Example:
Selectivity of adrenergic modulators for β-adrenoceptors over α-adrenoceptors



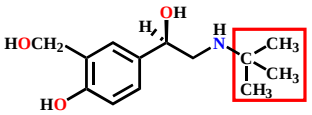
4.1 Vary Alkyl Substituents

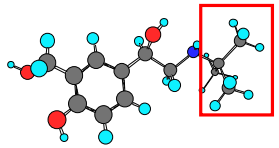
Adrenaline



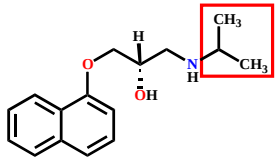


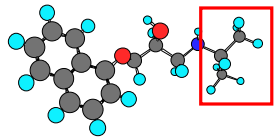
Salbutamol (Ventolin)
(Anti-asthmatic)





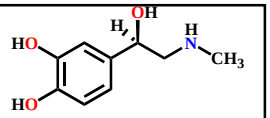
Propranolol
(β-Blocker)

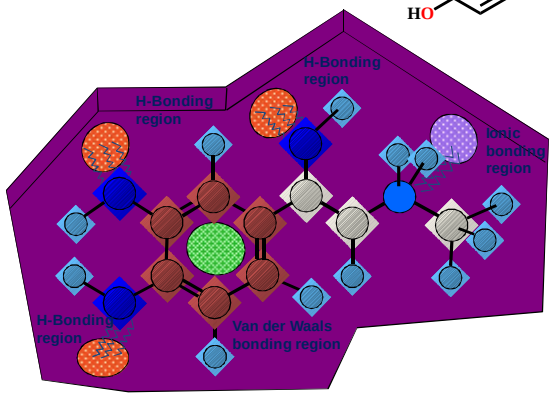




antihypertenzivum, antiarytmikum

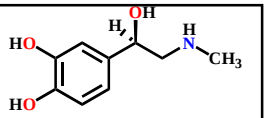
α-Adrenoceptor

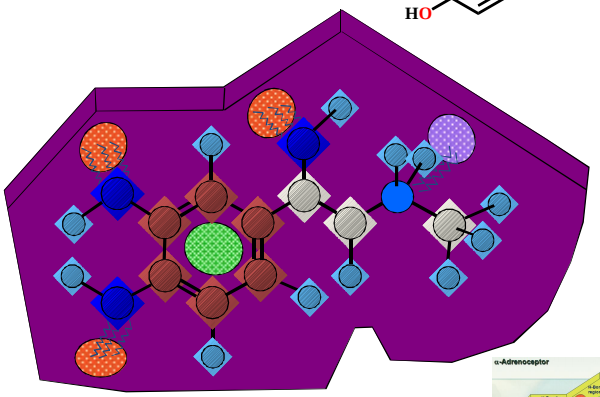


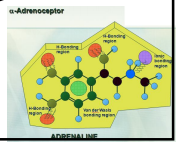


ADRENALINE

β-Adrenoceptor

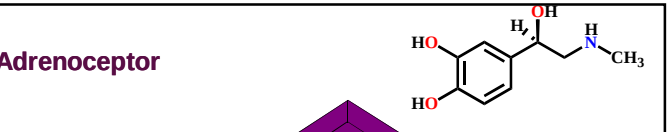


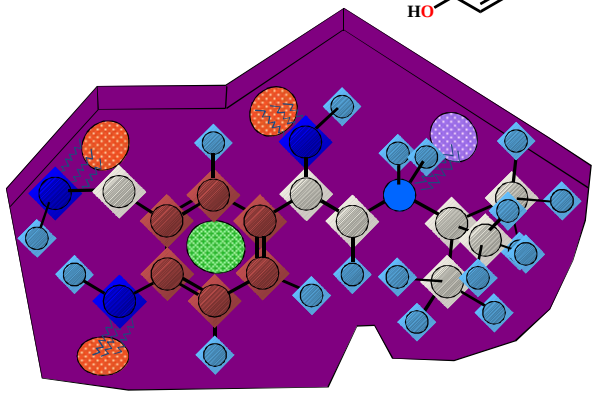




ADRENALINE

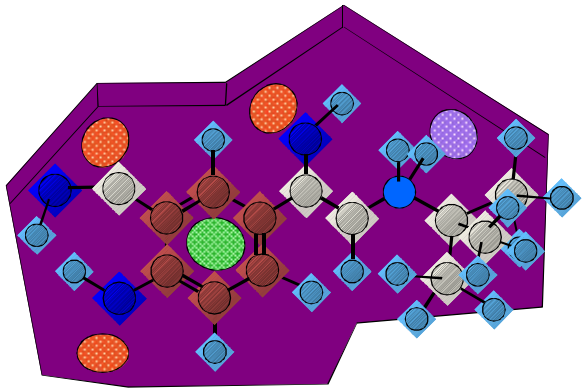
β-Adrenoceptor





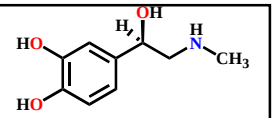
SALBUTAMOL

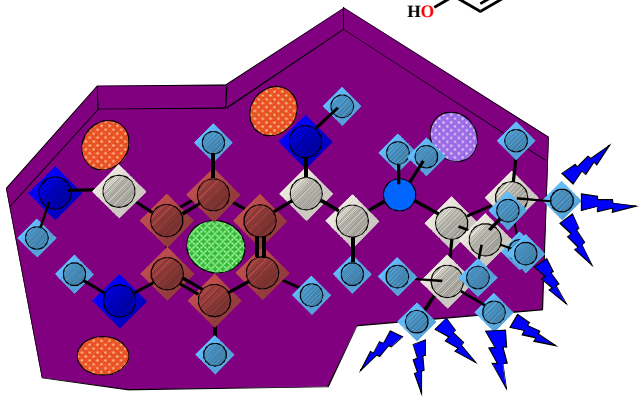
α-Adrenoceptor



SALBUTAMOL

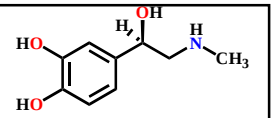
α-Adrenoceptor

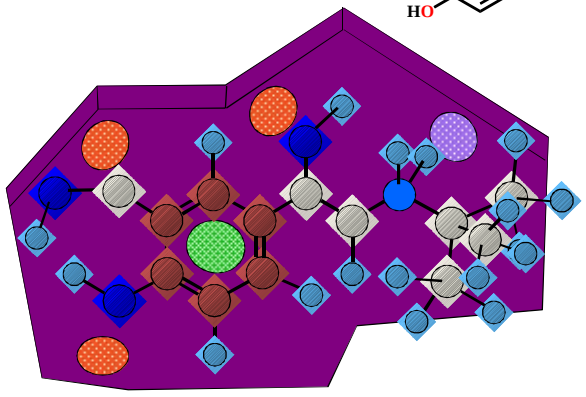




SALBUTAMOL

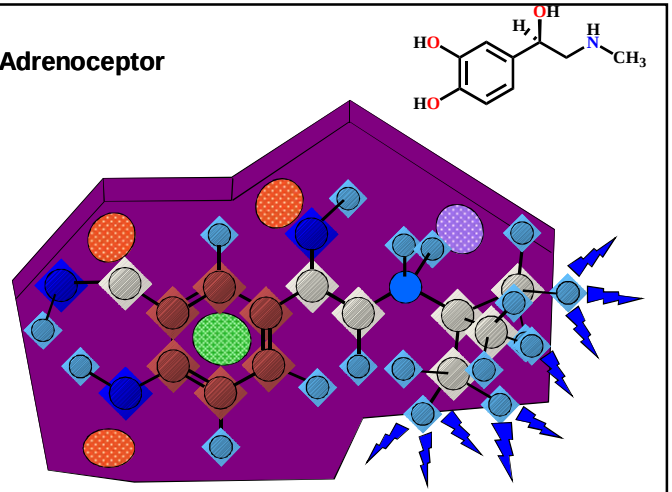
α-Adrenoceptor





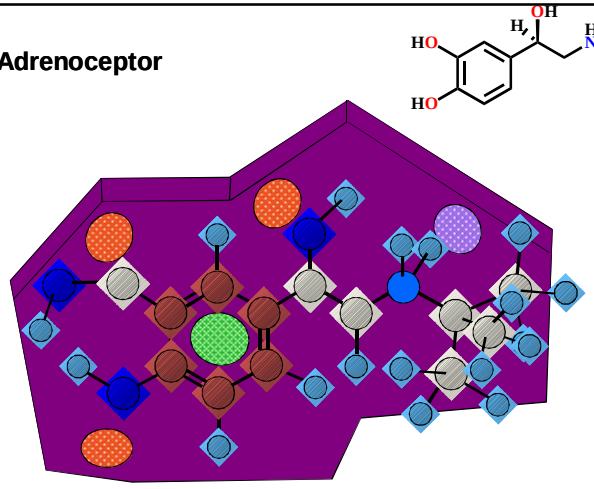
SALBUTAMOL

α-Adrenoceptor



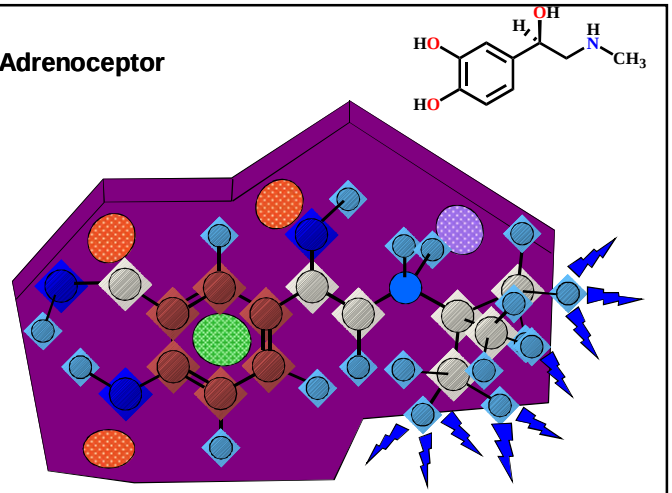
SALBUTAMOL

α-Adrenoceptor



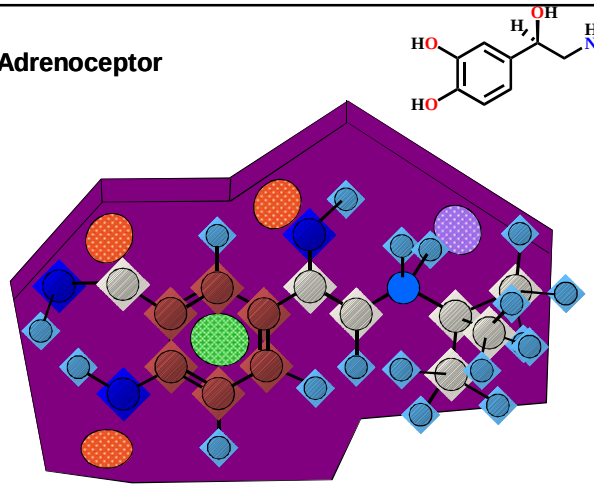
SALBUTAMOL

α-Adrenoceptor



SALBUTAMOL

α-Adrenoceptor



SALBUTAMOL

4.1 Vary Alkyl Substituents

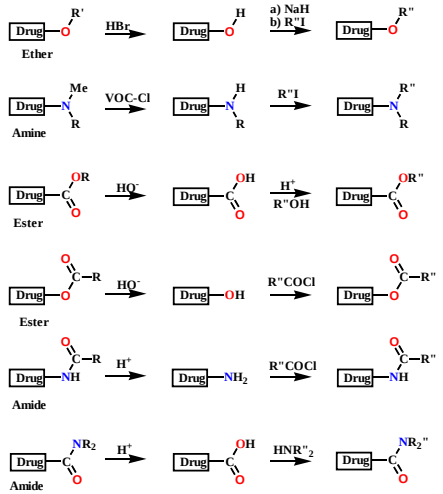
Notes on synthetic feasibility of analogues

- Feasible to remove alkyl substituents on heteroatoms and replace with other alkyl substituents
- Difficult to modify alkyl substituents on the carbon skeleton of a lead compound. Full synthesis is usually required

  (or coupling reactions)

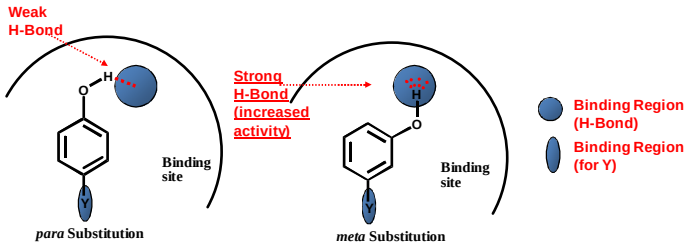
4.1 Vary Alkyl Substituents

Methods



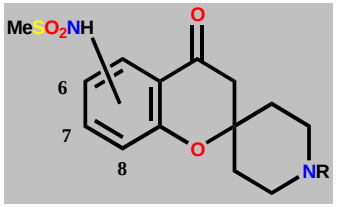
4.2 Vary Aryl Substituents

- vary substituents or substitution pattern



4.2 Vary Aryl Substituents

Vary substitution pattern to enhance binding interactions

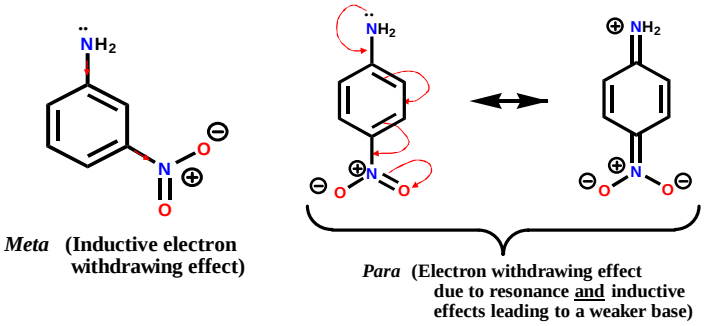


Benzopyrans

Anti-arrhythmic activity best when substituent is at 7-position

4.2 Vary Aryl Substituents

vary substitution pattern to **enhance binding strength indirectly - electronic effects**



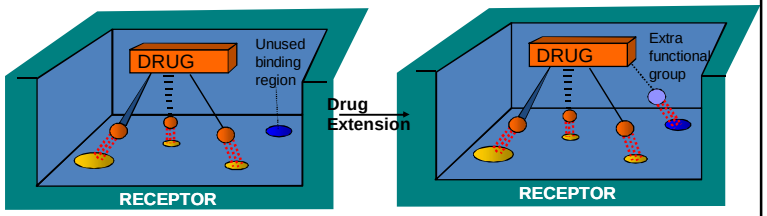
Meta (Inductive electron withdrawing effect)

Para (Electron withdrawing effect due to resonance and inductive effects leading to a weaker base)

binding strength of NH_2 as HBD affected by relative position of NO_2
stronger when NO_2 is at *para* position

4.3 Extension - Extra Functional Groups

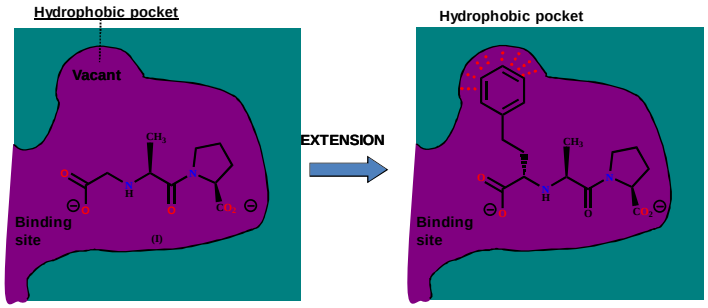
Rationale : To explore target binding site for further binding regions to achieve additional binding interactions



Binding regions
Binding group

4.3 Extension - Extra Functional Groups

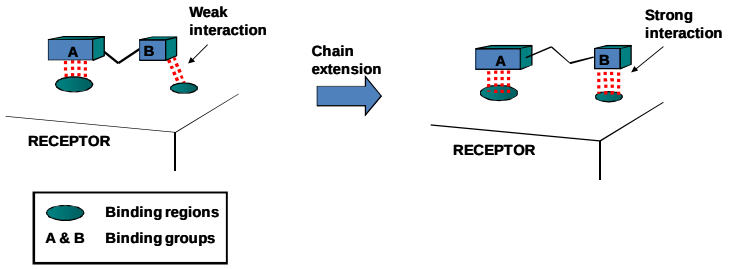
Example : ACE Inhibitors



4.4 Chain Extension / Contraction

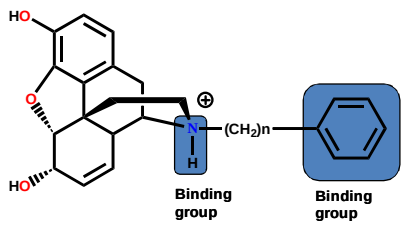
Rationale :

- vary length of chain to optimise interactions if a chain is connecting two binding groups



4.4 Chain Extension / Contraction

Example: ***N*-Phenethylmorphine**

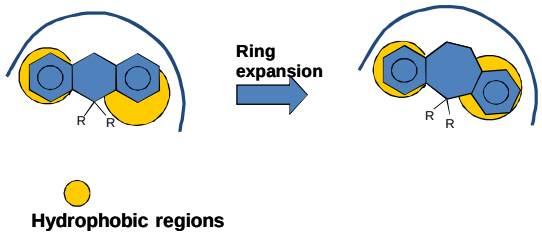


Optimum chain length = 2

4.5 Ring Expansion / Contraction

Rationale :

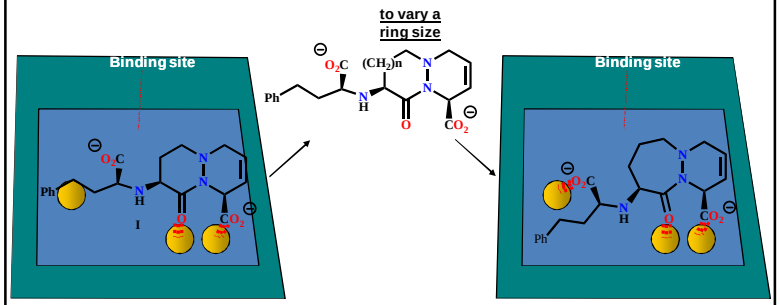
To improve overlap of binding groups with their binding regions



Hydrophobic regions

4.5 Ring Expansion / Contraction

Example

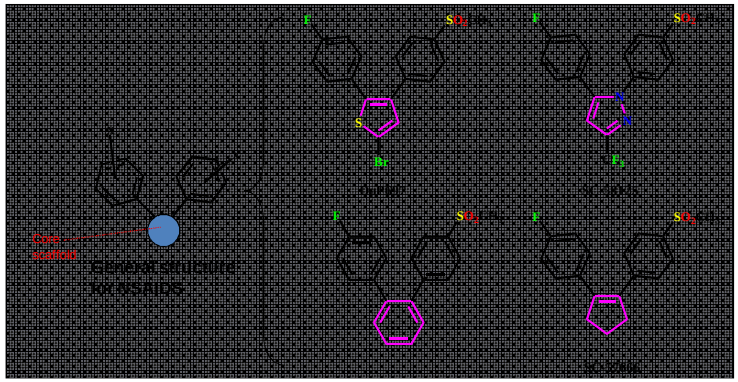


Binding regions

4.6 Ring Variations

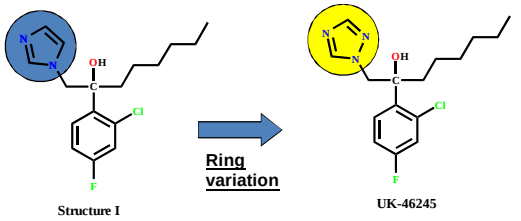
Rationale :

- replace aromatic ring with other ring
- often done for patent reasons (or mee too approach)



4.6 Ring Variations

sometimes results in improved properties



Structure I

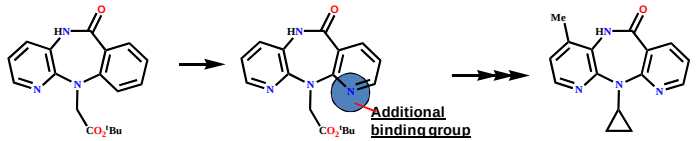
Antifungal agent

UK-46245

Improved selectivity against fungal enzyme

4.6 Ring Variations

Example - Nevirapine (antiviral agent)

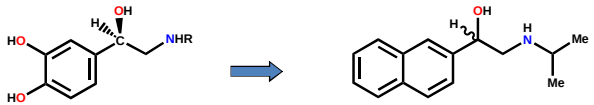


Lead compound

Nevirapine

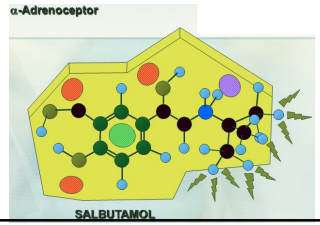
4.6 Ring Variations

Example - Pronethalol (β-blocker)



R = Me Adrenaline
R = H Noradrenaline

Pronethalol



Selective for β-receptors over α-receptors

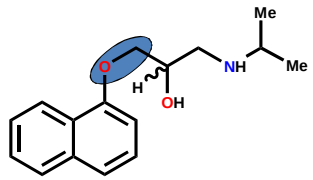
4.7 Isosteres and Bioisosteres

Isosteres:

- Replace a functional group with a group of same valency (isostere) e.g.-OH replaced by -SH, $-NH_2$, $-CH_3$
  -O- replaced by -S-, -NH-, $-CH_2-$
- Leads to more controlled changes in steric/electronic properties
- May affect binding and / or stability

4.7 Isosteres and Bio-isosteres

Useful for SAR



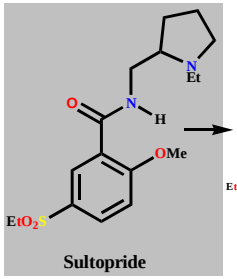
Propranolol (β-blocker)

- Replacing $-OCH_2-$ with $-CH=CH-$, $-SCH_2-$, $-CH_2CH_2-$ eliminates activity
- Replacing $-OCH_2-$ with $-NHCH_2-$ retains activity
- Implies O involved in binding (HBA)

4.7 Isosteres and Bio-isosteres

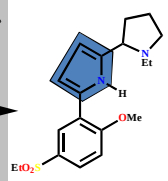
Bioisosteres:

- replace a functional group with another group which retains the same biological activity
- not necessarily the same valency



Sultopride

antipsychotic



DU 122290

Pyrrole ring = bioisostere for amide group

Improved selectivity for D_3 receptor over D_2 receptor

Optimalizácia štruktúry liečiva simplifikácia

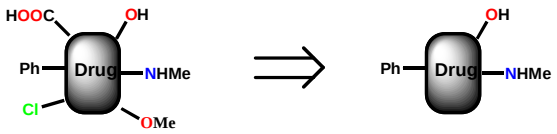
4.8 Simplification

Rationale :

- Lead compounds from natural sources are often complex and difficult to synthesise
- Simplifying the molecule makes synthesis of analogues easier, quicker and cheaper
- Simpler structures may fit binding site easier and increase activity
- Simpler structures may be less toxic if excess functional groups removed

4.8 Simplification

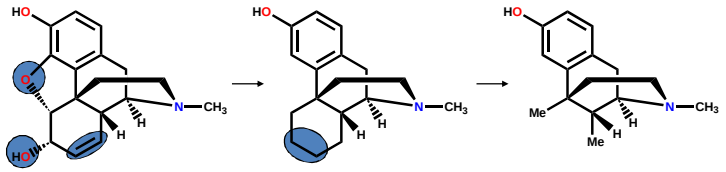
- retain pharmacophore
- remove unnecessary functional groups



4.8 Simplification

- Remove excess rings

Example

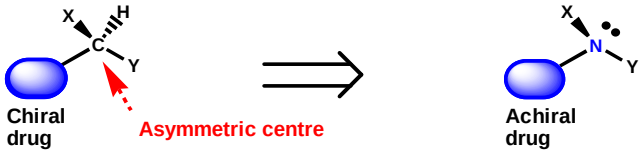


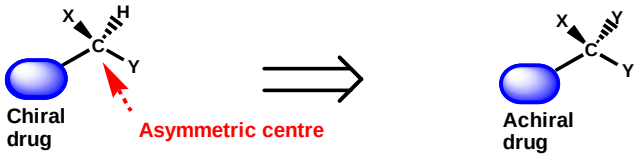
Excess functional groups Excess ring

opioid analgesic

4.8 Simplification

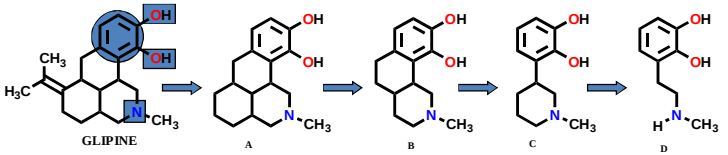
- Remove stereogenic centres





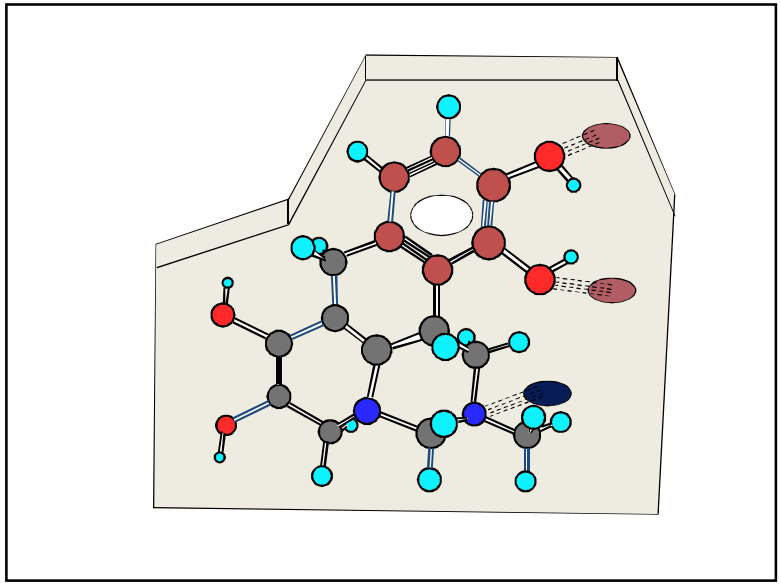
4.8 Simplification

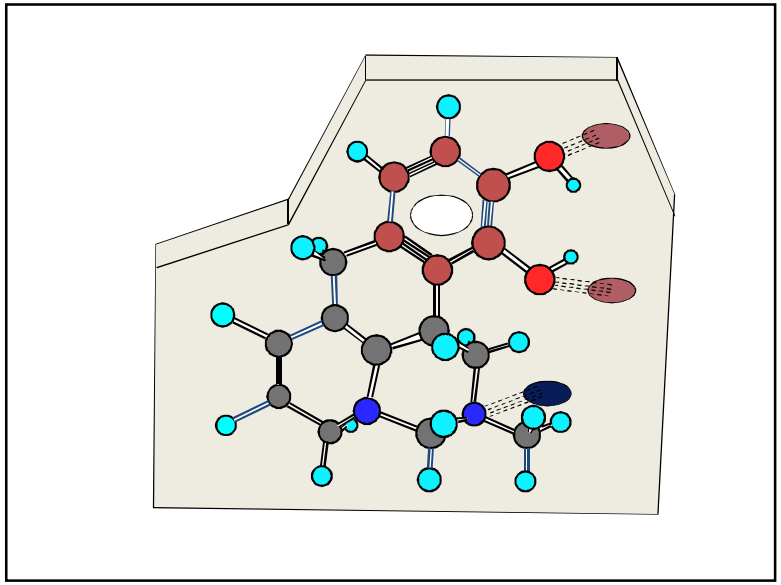
- Simplify in stages to avoid oversimplification

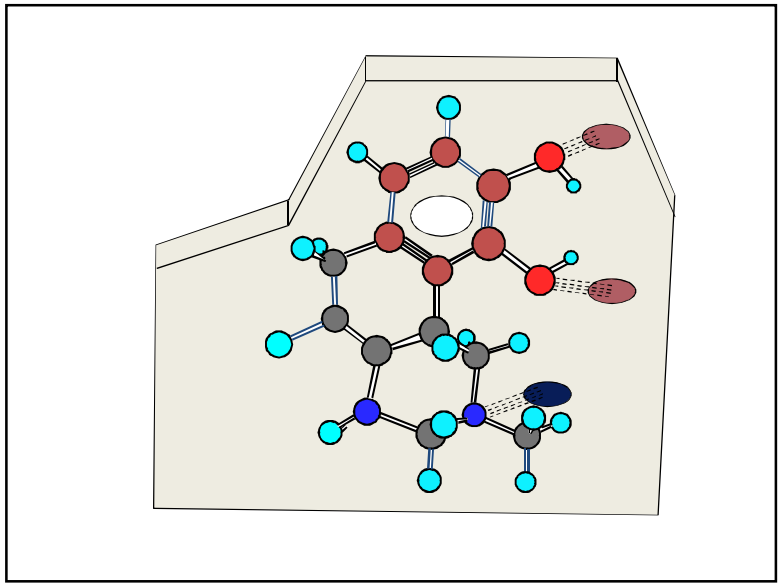


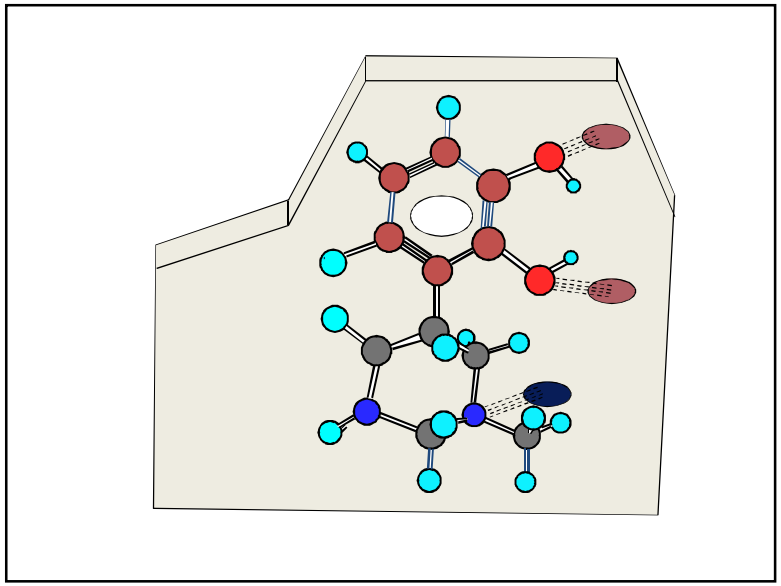
Pharmacophore

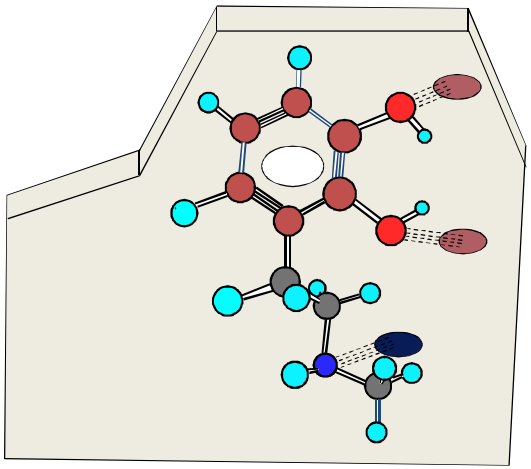
- Simplification does not mean 'pruning groups' off the lead compound
- Compounds usually made by total synthesis





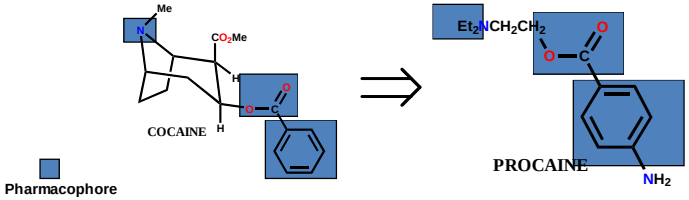






4.8 Simplification

Example



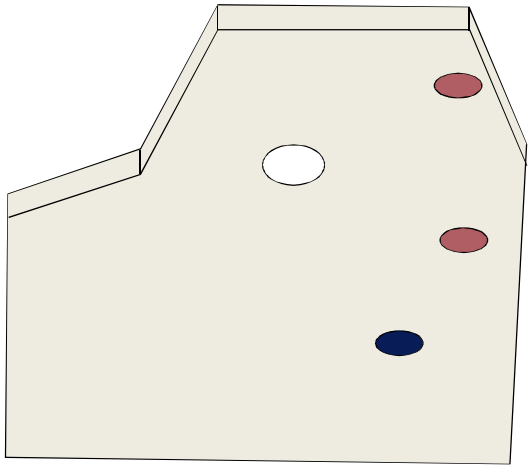
- important binding groups retained
- unnecessary ester removed
- complex ring system removed

4.8 Simplification

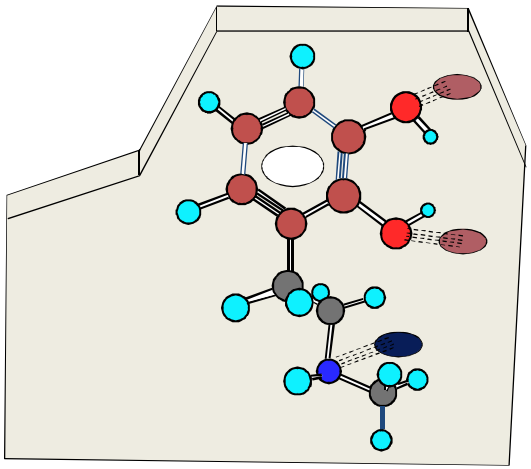
Disadvantages:

- oversimplification may result in decreased activity and selectivity
- simpler molecules can have more conformations
- more likely to interact with more than one target binding site

  (off target toxicity)

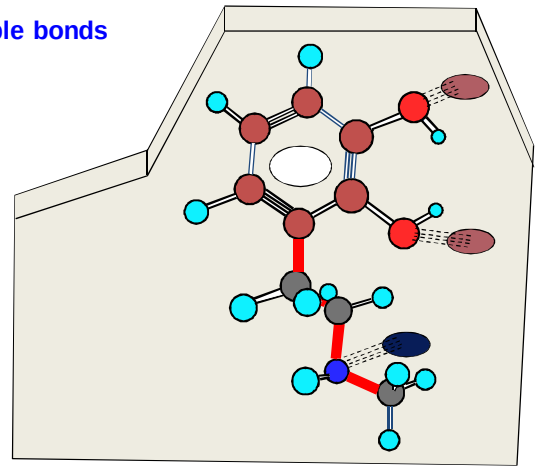


Target binding site



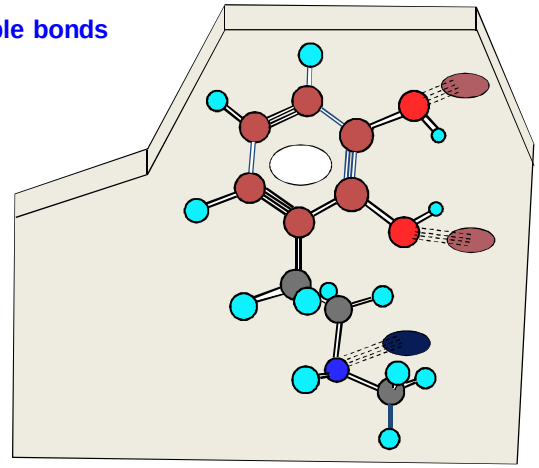
Target binding site

Rotatable bonds



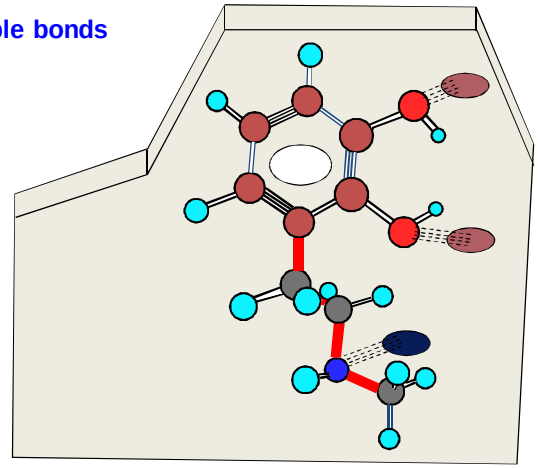
Target binding site

Rotatable bonds



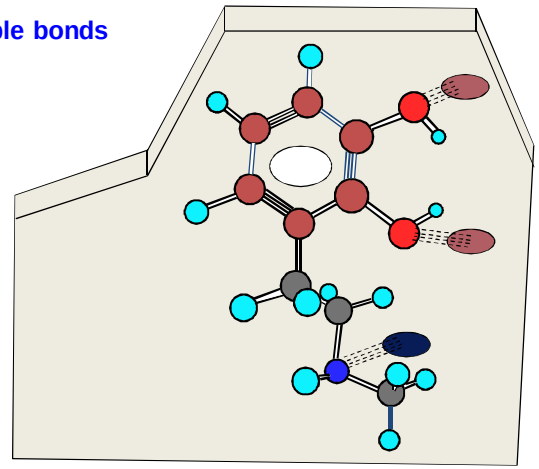
Target binding site

Rotatable bonds



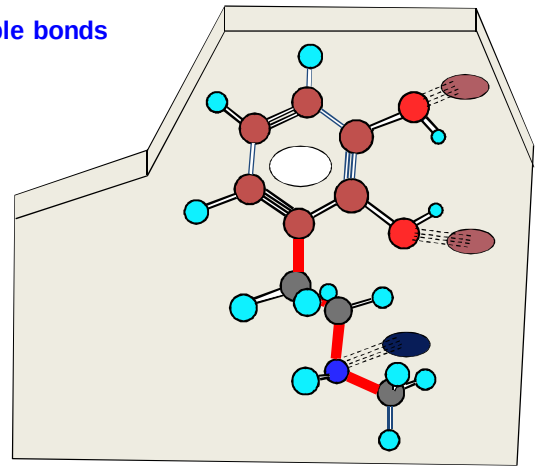
Target binding site

Rotatable bonds



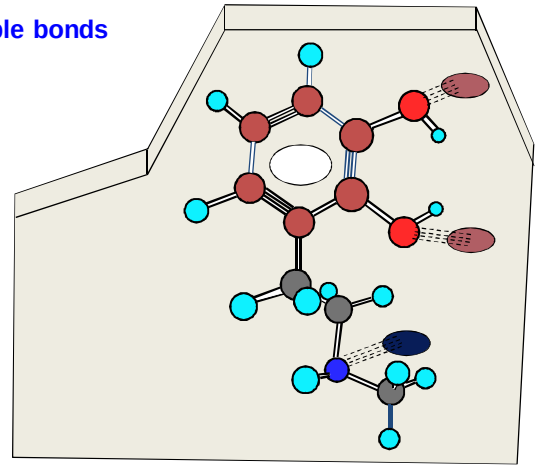
Target binding site

Rotatable bonds



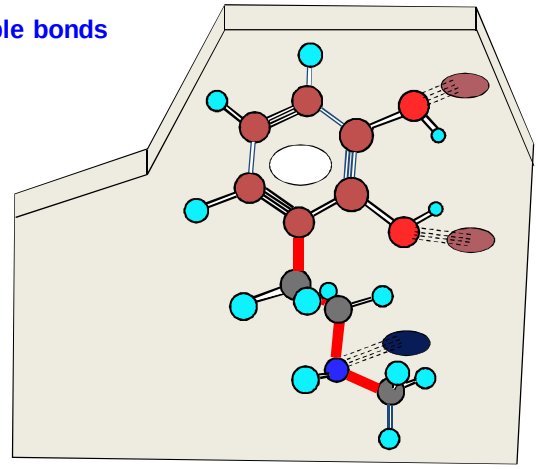
Target binding site

Rotatable bonds



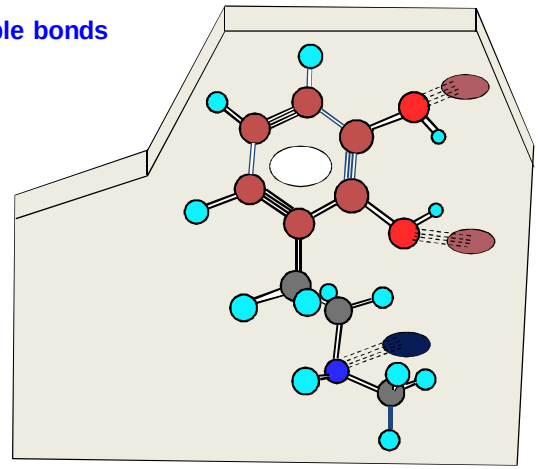
Target binding site

Rotatable bonds



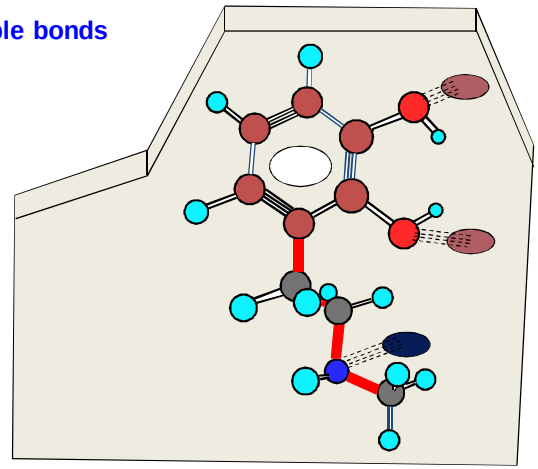
Target binding site

Rotatable bonds



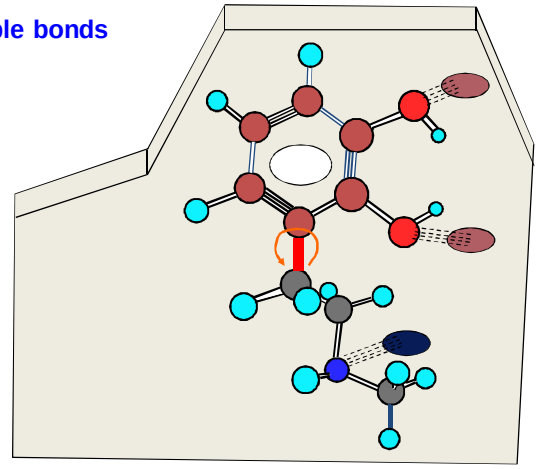
Target binding site

Rotatable bonds



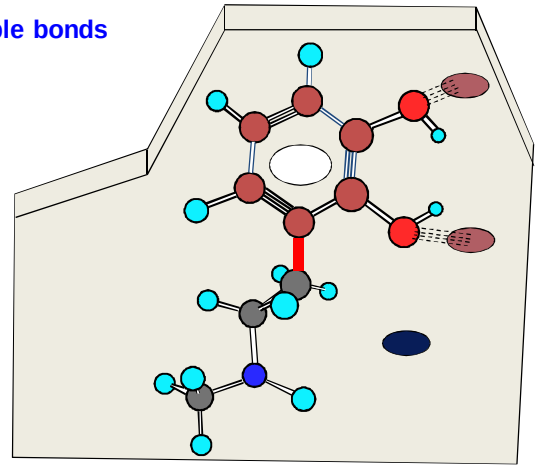
Target binding site

Rotatable bonds



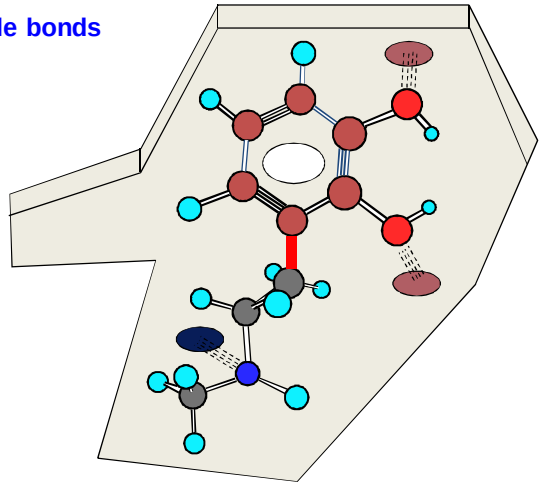
Target binding site

Rotatable bonds



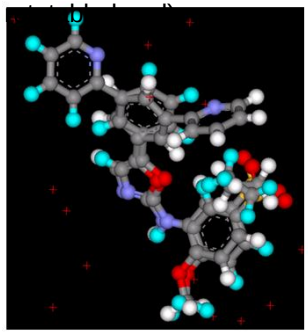
Target binding site

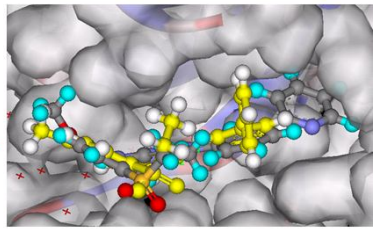
Rotatable bonds



Different binding site - side effects

PDB: 1Y6A complex AAZ / VEGFR2 TK (two conformers present due to a present





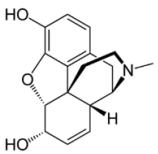
1Y6A-N2,N3

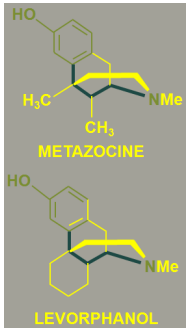
4.8 Simplification

Example of oversimplification

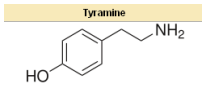
- Simplification of opiates

MORPHINE

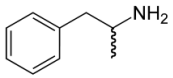




TYRAMINE

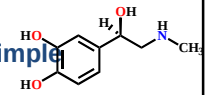


AMPHETAMINE

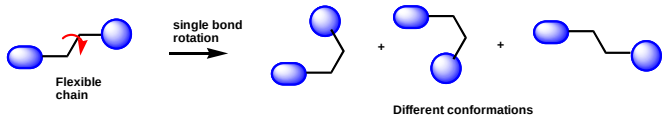


OVERSIMPLIFICATION

4.9 Rigidification



- endogenous lead compounds are often simple and flexible (e.g. adrenaline)
- fit several targets due to different active conformations (e.g. adrenergic receptor types and subtypes)

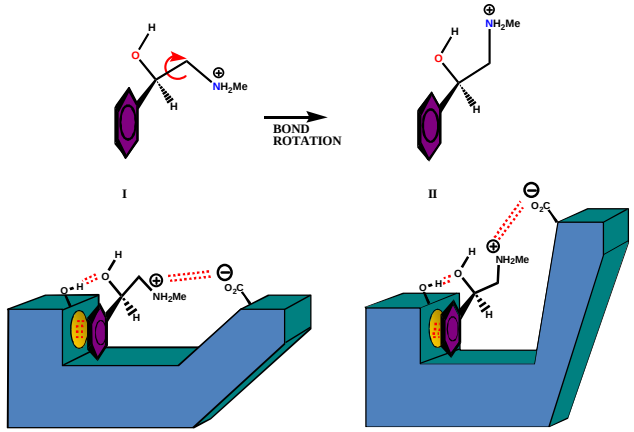


- Rigidify molecule to limit conformations => conformational restraint
  - Increases activity (more chance to be in desired active conformation)
  - Increases selectivity (less chance of undesired active conformations responsible for non selectivity)

Disadvantage:

- molecule is more complex and may be more difficult to synthesise

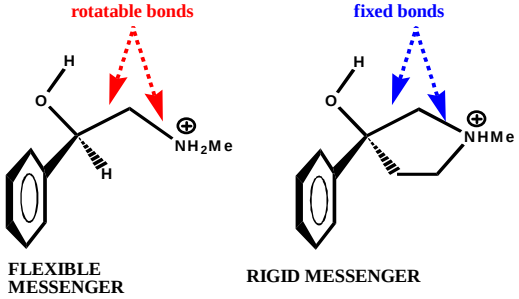
4.9 Rigidification



4.9 Rigidification

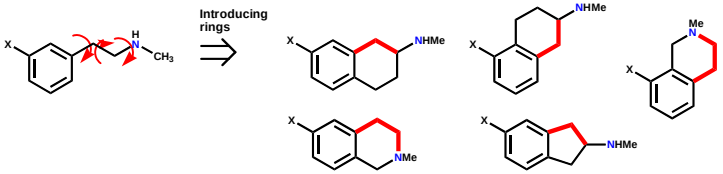
Introduce ring

bonds within ring systems are locked and cannot rotate freely



4.9 Rigidification

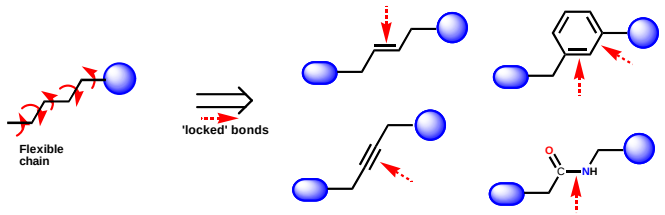
locked particular rotamers



test rigid structures to see which ones have retained active conformation

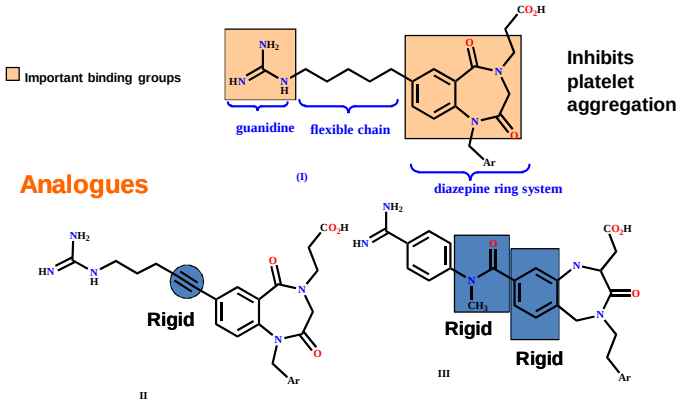
4.9 Rigidification

Introduce rigid functional groups



4.9 Rigidification

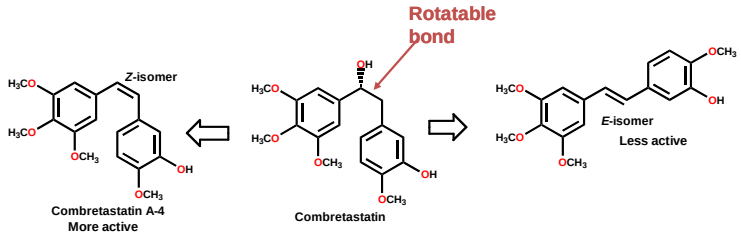
Examples



Analogues

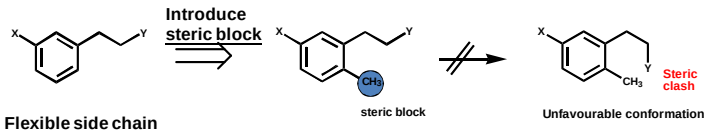
4.9 Rigidification

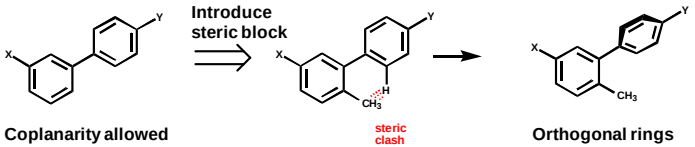
Examples - Combretastatin (anticancer agent)



4.9 Rigidification

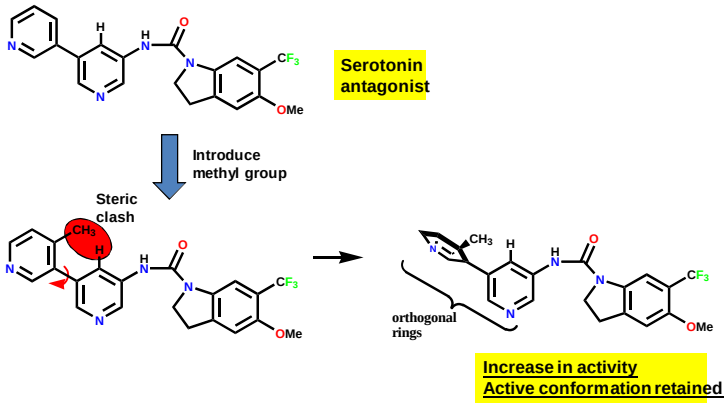
Methods - Steric Blockers





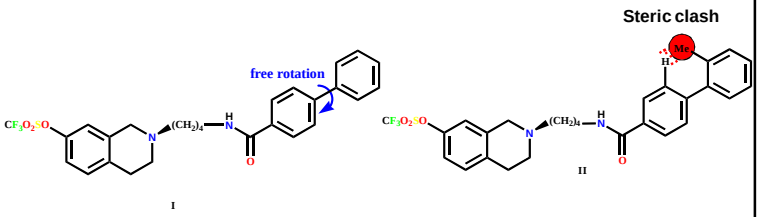
4.9 Rigidification

Steric Blockers - Examples



4.9 Rigidification

Steric Blockers - Examples



D_3 Antagonist

Inactive
Active conformation disallowed

Optimalizácia štruktúry liečiva štruktúrny design

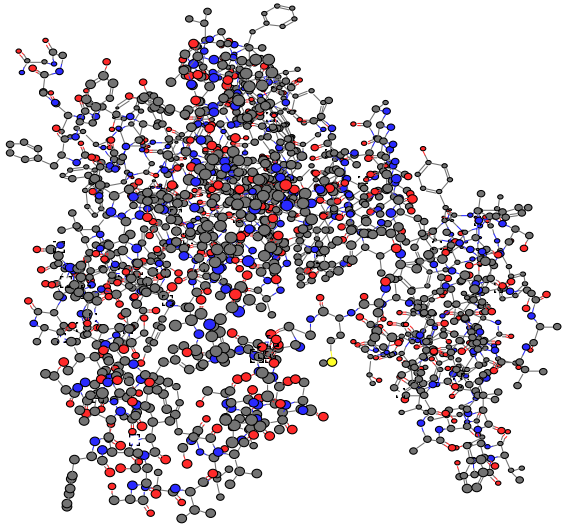
4.10 Structure based drug design

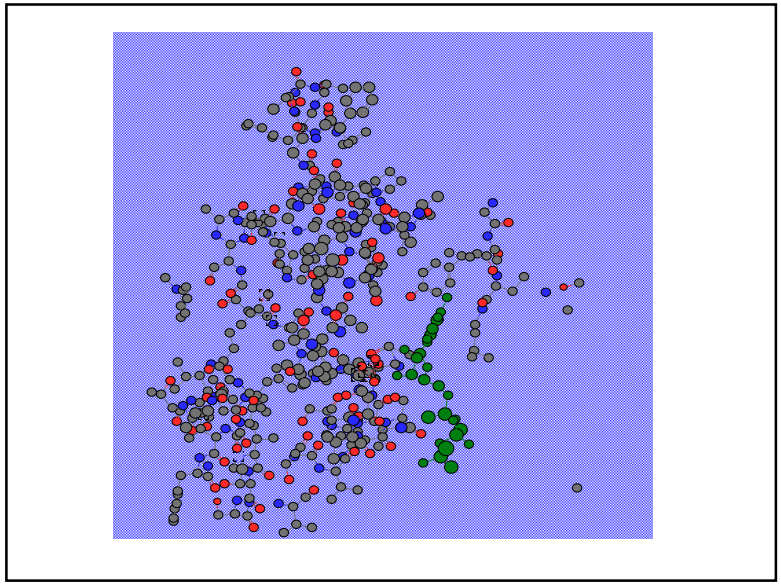
Strategy

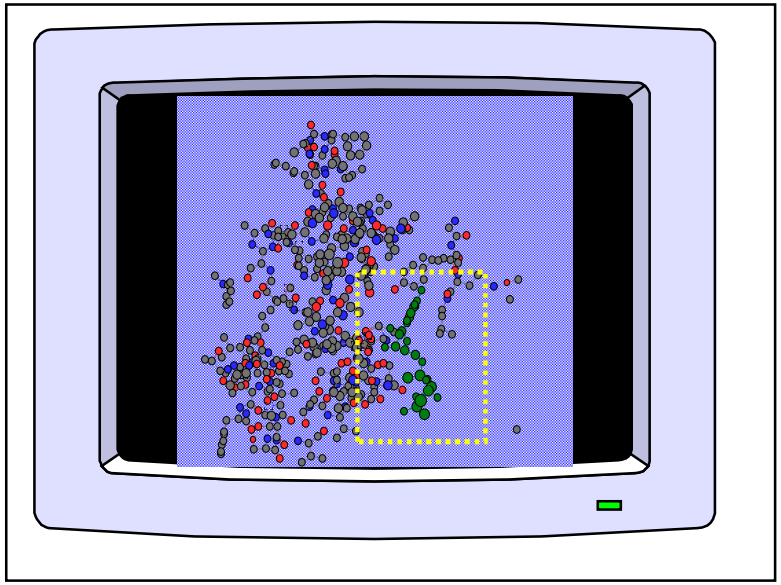
Carry out drug design based on the interactions between the lead compound and the target binding site

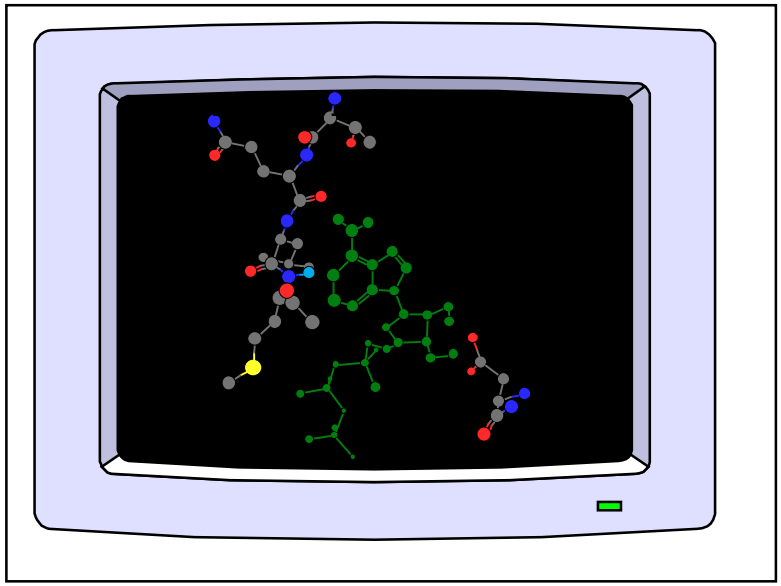
Procedure

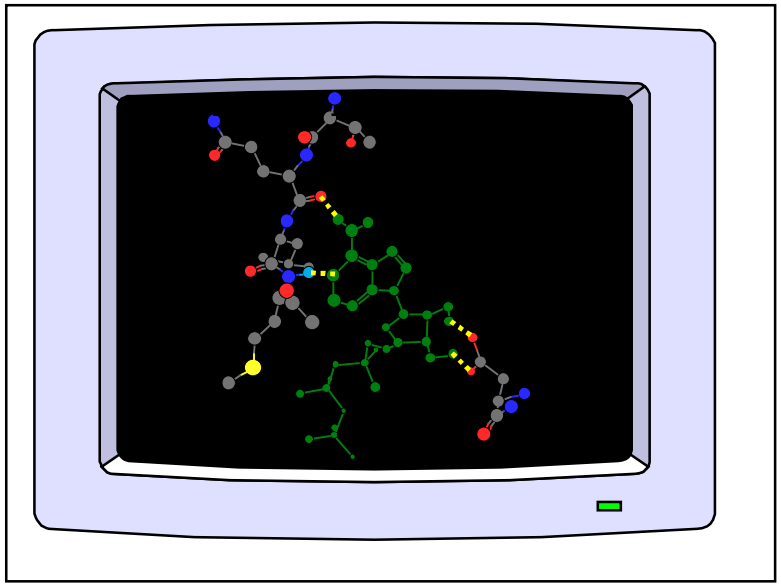
- Crystallise target protein with bound ligand (e.g. enzyme + inhibitor or ligand)
- Acquire structure by X-ray crystallography
- Identify binding site (region where ligand is bound)
- Identify binding interactions between ligand and target (modelling)
- Identify vacant regions for extra binding interactions (modelling)
- 'Fit' analogues into binding site to test binding capability (modelling)

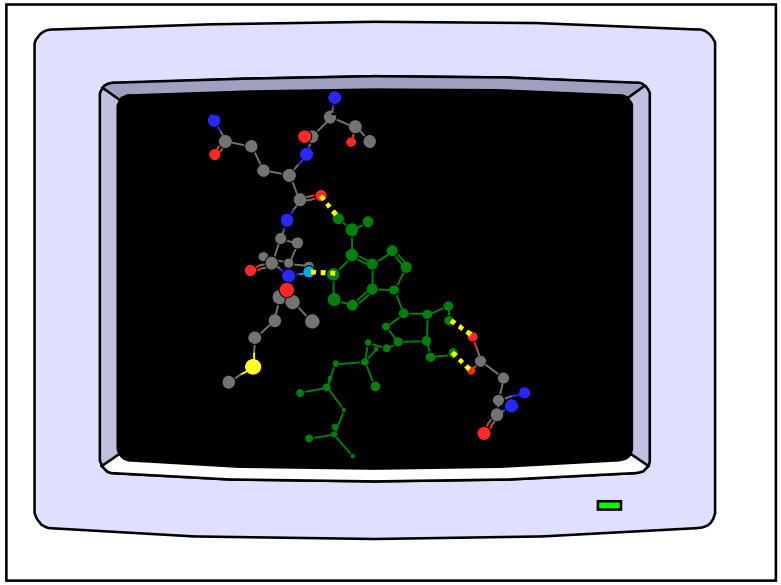


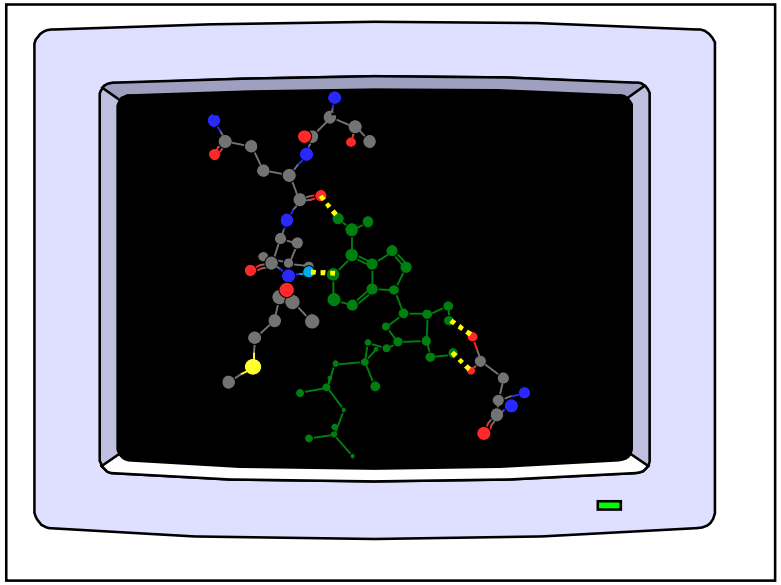


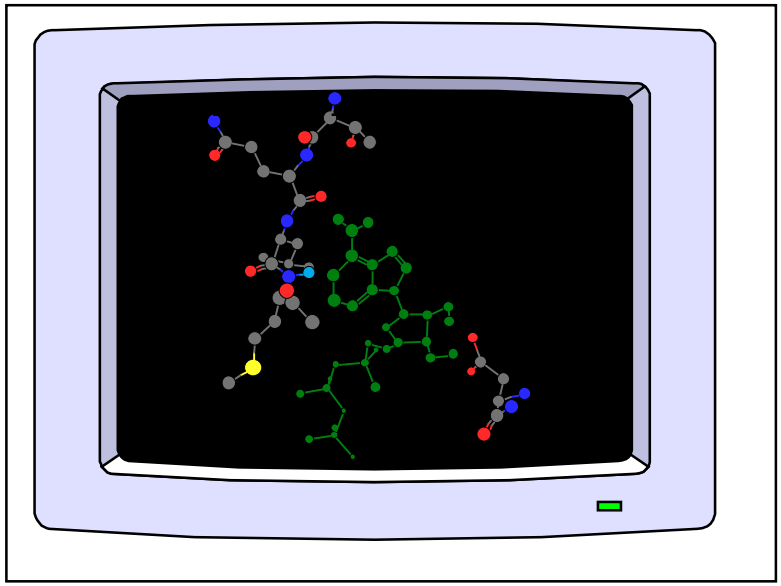


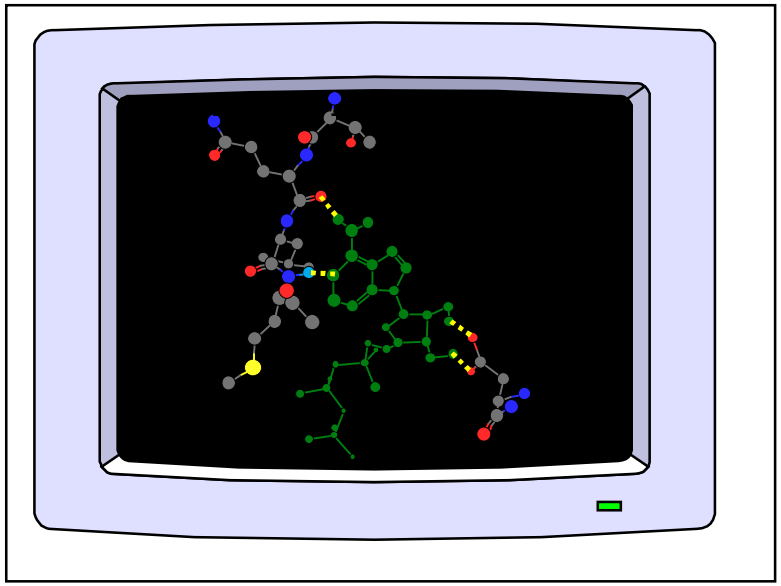


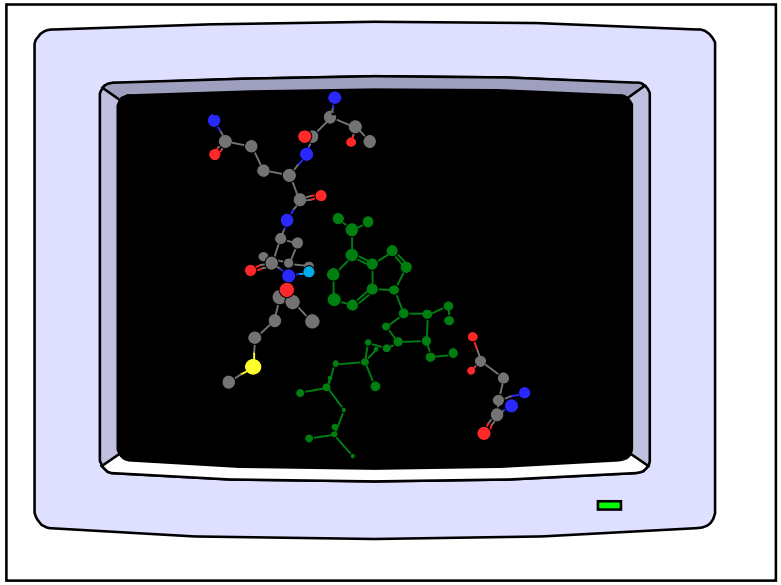


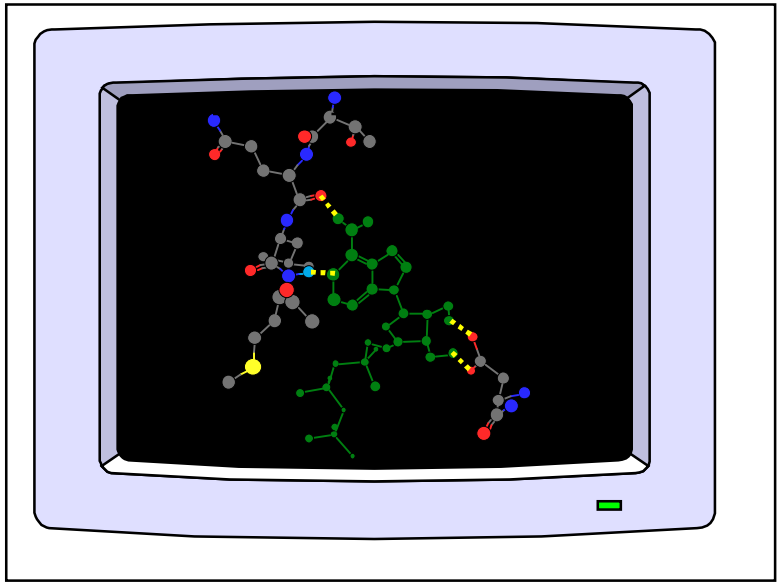


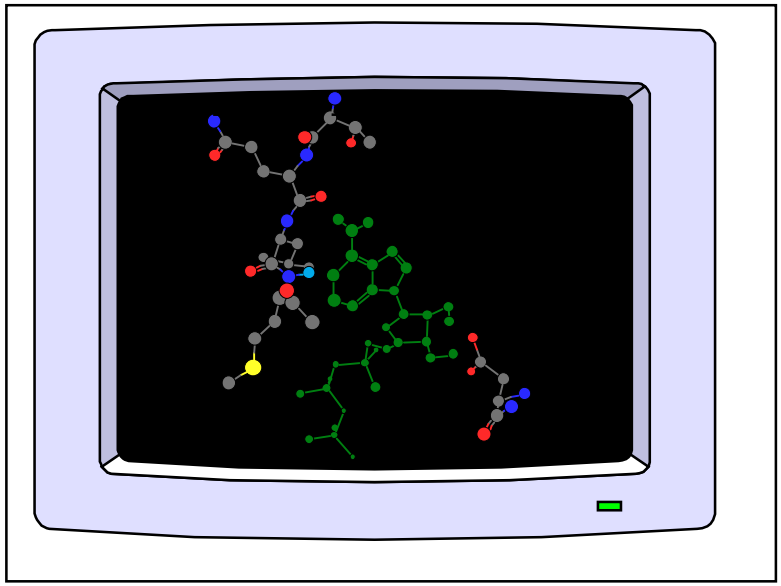


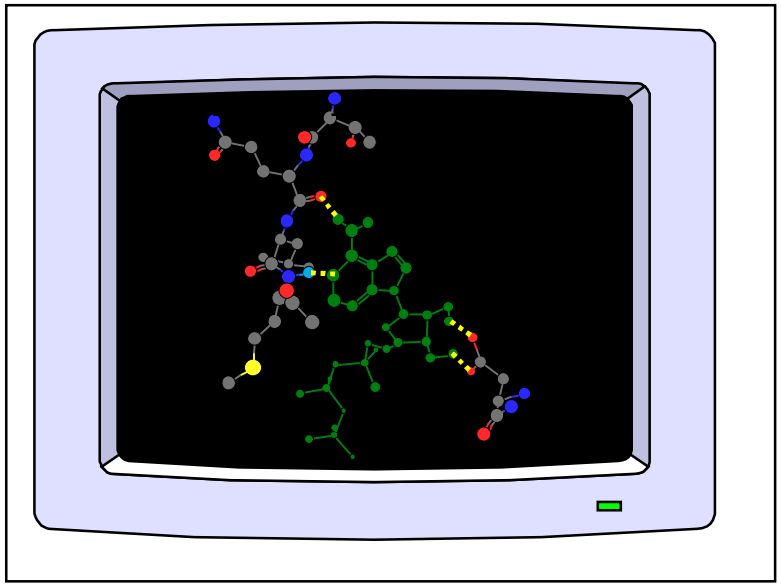


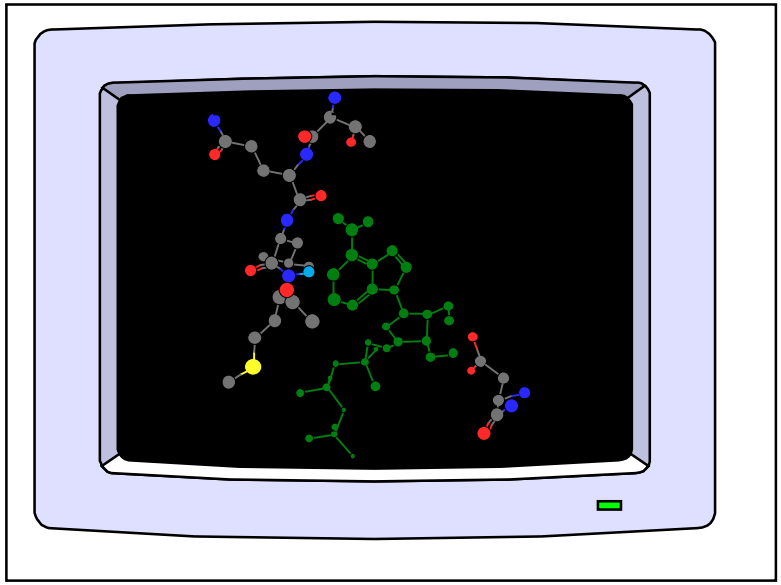


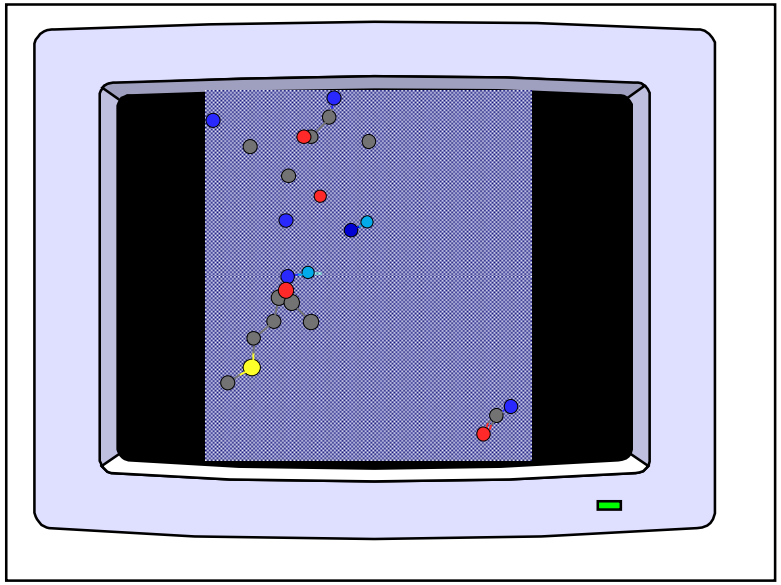






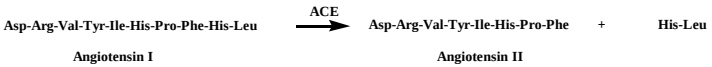






4.10 Structure based drug design

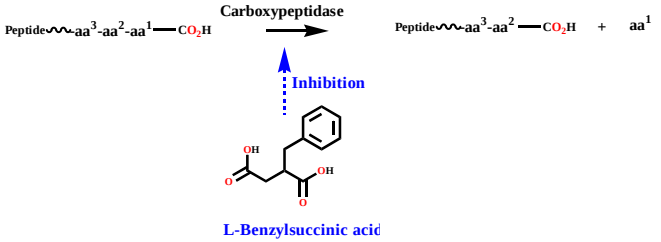
Design of Antihypertensives - ACE inhibitors



- ACE = Angiotensin converting enzyme
- Angiotensin II - hormone which stimulates constriction of blood vessels - causes rise in blood pressure
- ACE inhibitors - useful antihypertensive agents
- ACE - membrane bound zinc metalloproteinase not easily crystallised
- Study analogous enzyme which can be crystallised

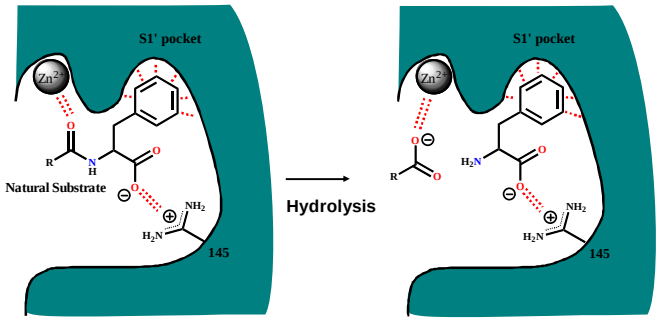
4.10 Structure based drug design

Carboxypeptidase



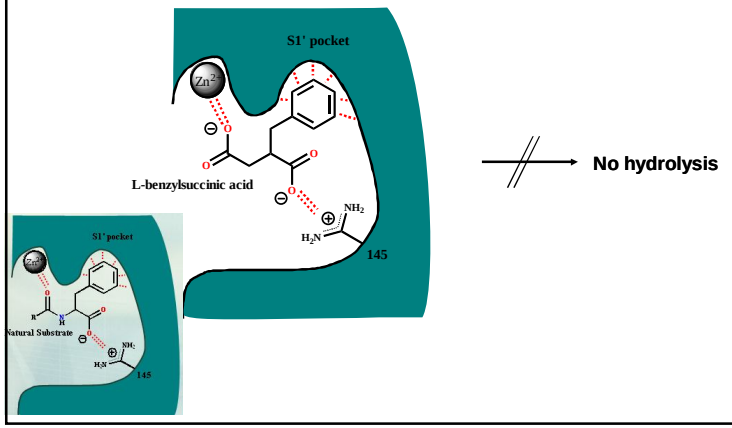
4.10 Structure based drug design

Carboxypeptidase mechanism



4.10 Structure based drug design

Inhibition of carboxypeptidase

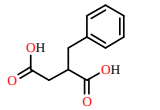


4.10 Structure based drug design

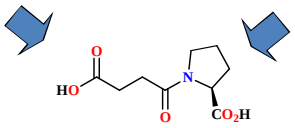
Lead compounds for ACE inhibitor

Glu-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro

Teprotide



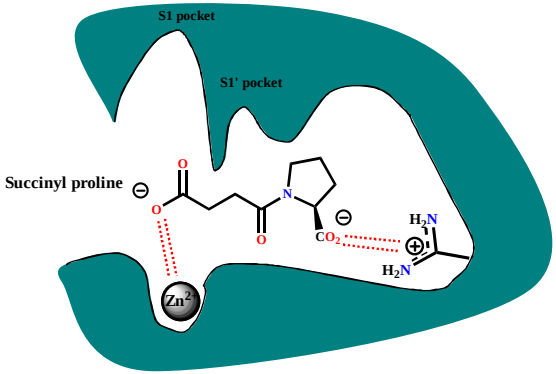
L-Benzylsuccinic acid



Succinyl proline

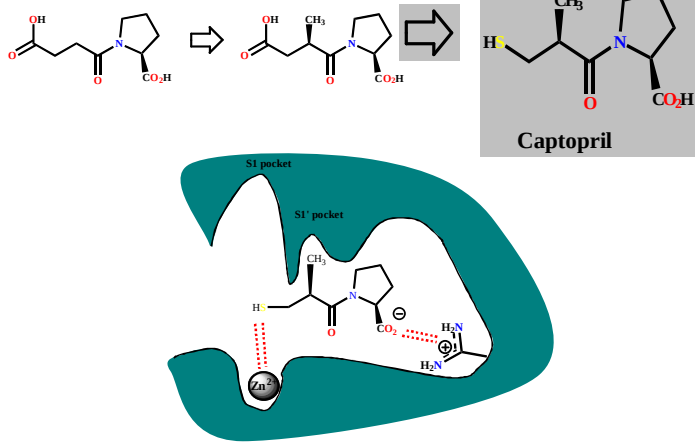
4.10 Structure based drug design

Proposed binding mode



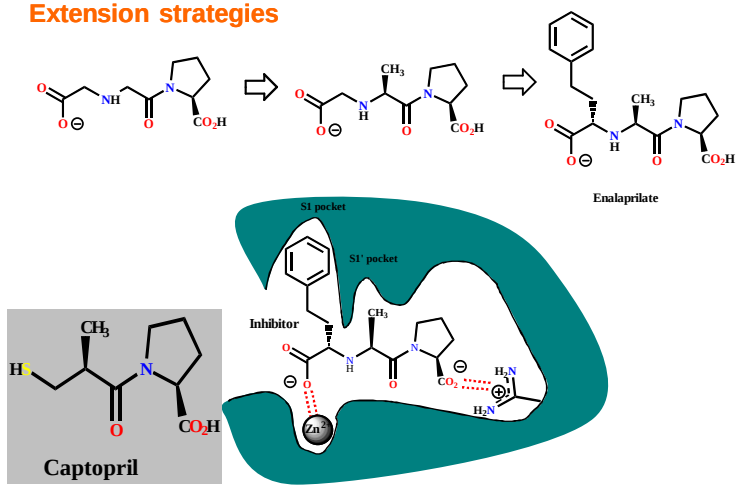
4.10 Structure based drug design

Extension and bioisostere strategies



4.10 Structure based drug design

Extension strategies



4.11 De Novo Drug Design

The design of novel agents based on a knowledge of the target binding site

Procedure

- Crystallise target protein with bound ligand
- (e.g. enzyme + inhibitor or ligand)
- Acquire structure by X-ray crystallography
- Identify binding site (region where ligand is bound)
- Remove ligand
- Identify potential binding regions in the binding site
- Design a lead compound to interact with the binding site

- Synthesise the lead compound and test it for activity
- Crystallise the lead compound with target protein and identify the actual binding interactions
- Structure based drug design