OPTIMIZING TARGET INTERACTIONS

Drug design and development

Stages:

1) Identify target disease
2) Identify drug target
3) Establish testing procedures
4) Find a lead compound
5) Structure Activity Relationships (SAR)
6) Identify a pharmacophore
7) Drug design - optimising target interactions
8) Drug design - optimising pharmacokinetic properties
9) Toxicological and safety tests
10) Chemical development and production
11) Patenting and regulatory affairs
12) Clinical trials

Optimalizacia skeletu (obsah)

•**VARY ALKYL SUBSTITUENTS** zmena alkylových substituentov (zmena velkosti a rozvetvenia/aktivita a selektivita, lahke na heteroatomoch N,O, „de novo“ ak uhlikatom skelete)
•**VARY ARYL SUBSTITUENTS** zmena polohy arylových substituentov (regioizomery => aktivita lepsi prekryv, alebo elektronicky vplyv na ine skupiny => napr. zmena bazicity –NH2)
•**EXTENSION** zvacsenie molekuly => pridanie f. skupiny (aktivita)
•**CHAIN EXPANSION/CONTRACTION** zmena velkosti retazca => aktivita, selektivita
•**RING EXPANSION/CONTRACTION** (zmena polohy substituentov, lepsi prekryv s v. miestom)
•**RING VARIATION** zmena typu cyklu (selektivita, patentovanie “mee too”)
•**(BIO)ISOSTERIC REPLACEMENT** (aktivita, stabilita, synteza)
•**SIMPLIFICATION** zjednodusenie skeletu (prirodne latky, pozor na oversimplification a NRB)
•**RIGIDIFICATION** (stericky blokator, kruh, nasobna vazba, amidicka v., hladanie aktivnych konformacii, aktivita, selektivita)
•**STRUCTURE DESIGN** (X-ray, vazobne miesto a v. interakcie, vakantne domeny, modeling, optimalizacia a “de novo design“)

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

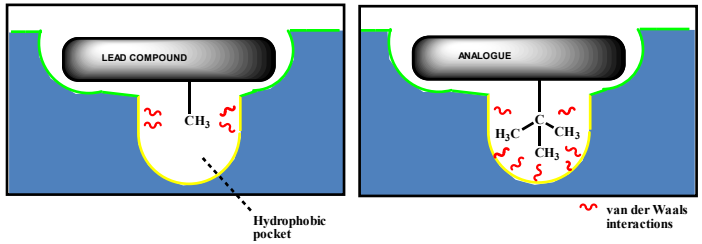
STRATEGIES

- Vary alkyl substituents
- Vary aryl substituents
- Ligand extension (addition of functional groups)
- Chain extensions / contractions
- Ring expansions / contractions
- Ring variation
- Isosteres
- Simplification
- Rigidification

Optimalizácia štruktúry liečiva
-
zmena alkylových substituentov

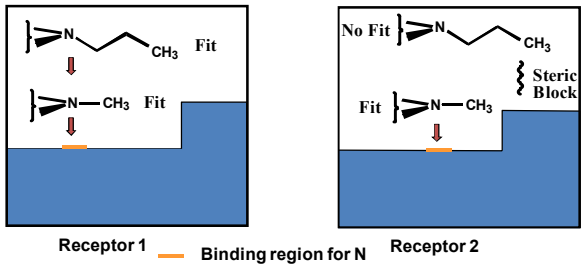
4.1 Vary Alkyl Substituents

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

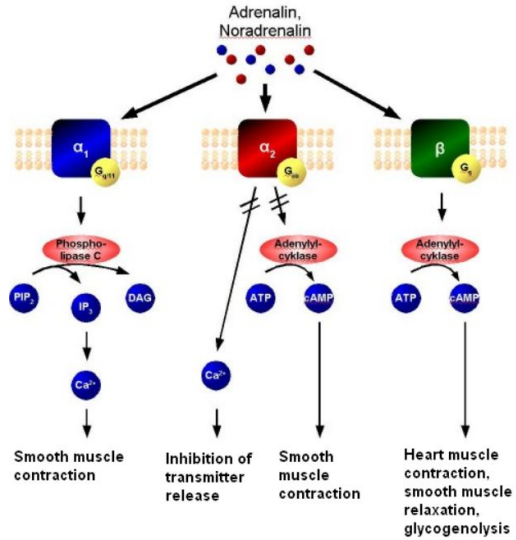


4.1 Vary Alkyl Substituents

vary length and bulk of alkyl group to introduce selectivity

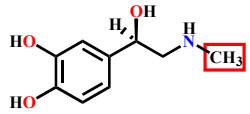


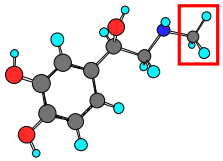
Example:
Selectivity of adrenergic modulators for β-adrenoceptors over α-adrenoceptors



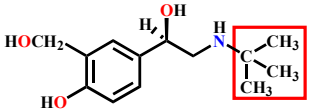
4.1 Vary Alkyl Substituents

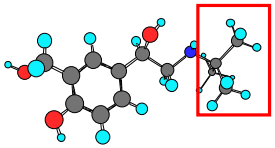
Adrenaline



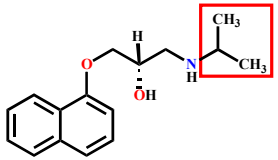


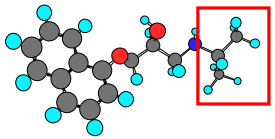
Salbutamol (Ventolin)
(Anti-asthmatic)





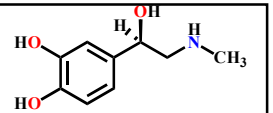
Propranolol
(β-Blocker)

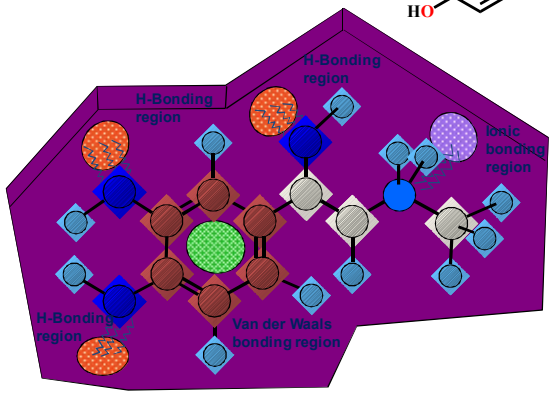




antihypertenzivum, antiarytmikum

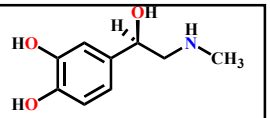
α-Adrenoceptor

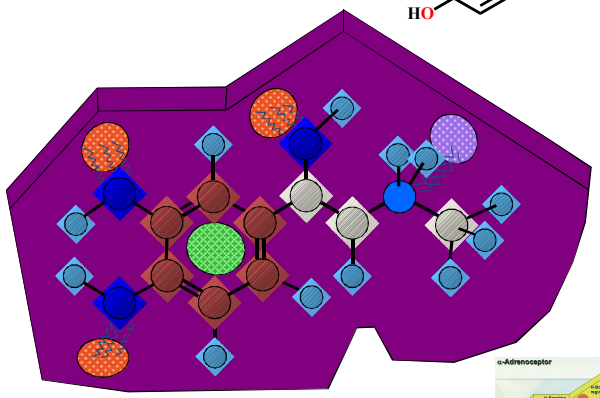




ADRENALINE

β-Adrenoceptor





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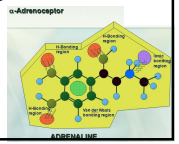
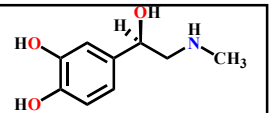
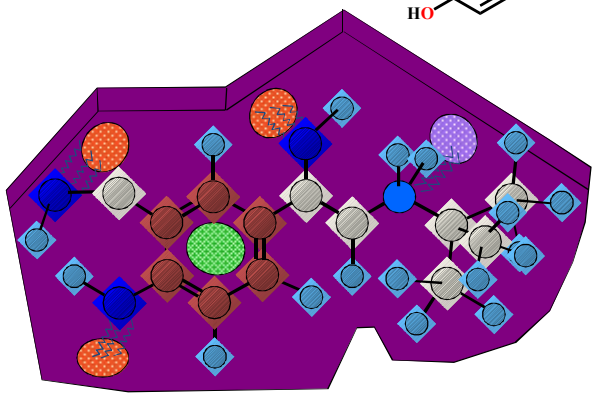


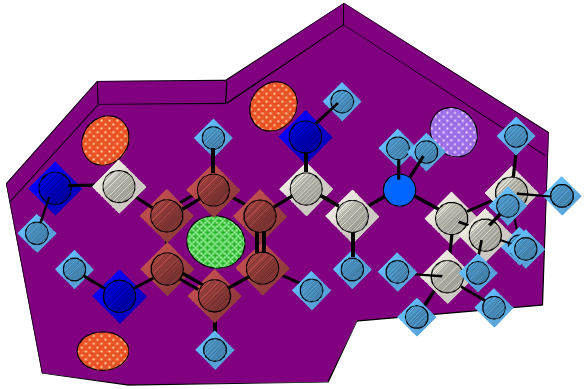
β-Adrenoceptor





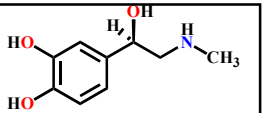
SALBUTAMOL

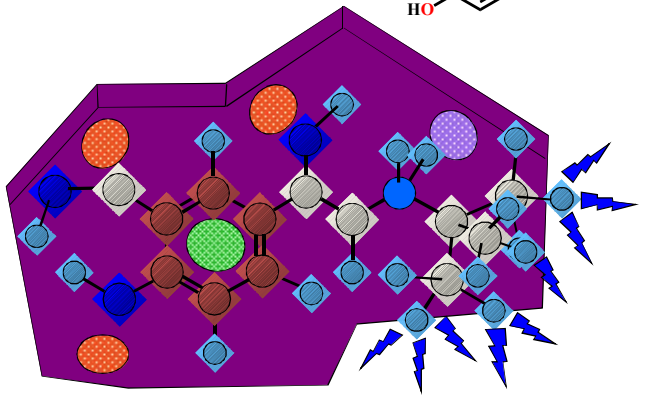
α-Adrenoceptor



SALBUTAMOL

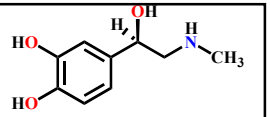
α-Adrenoceptor

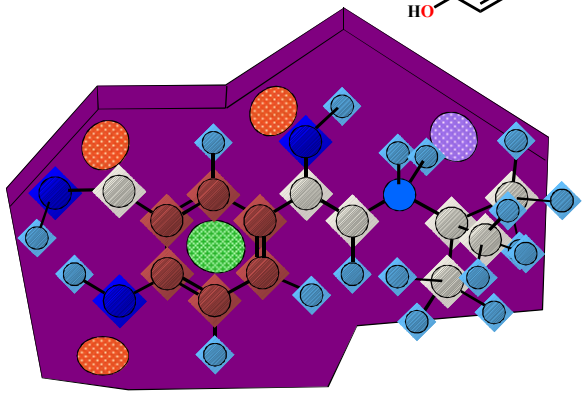




SALBUTAMOL

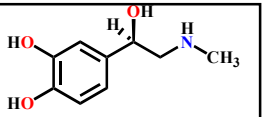
α-Adrenoceptor

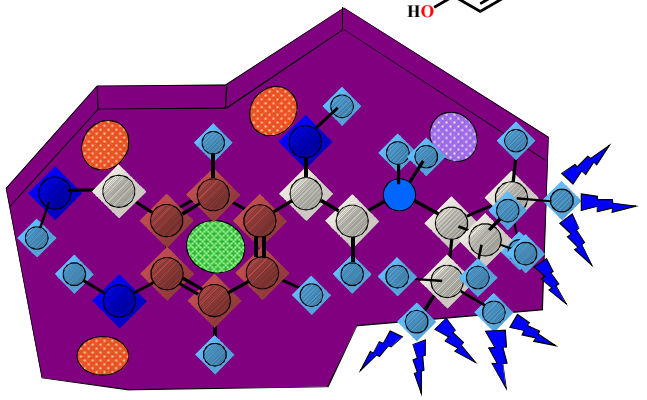




SALBUTAMOL

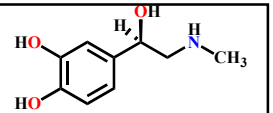
α-Adrenoceptor

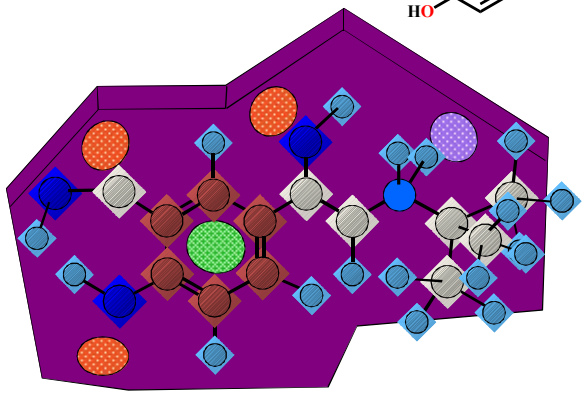




SALBUTAMOL

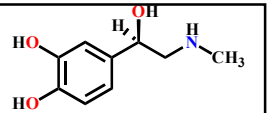
α-Adrenoceptor

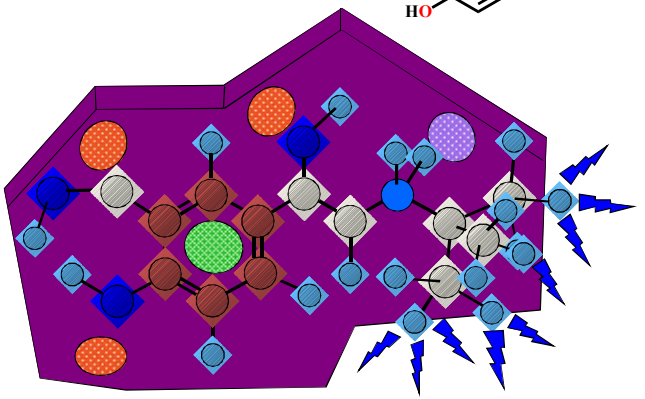




SALBUTAMOL

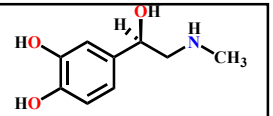
α-Adrenoceptor

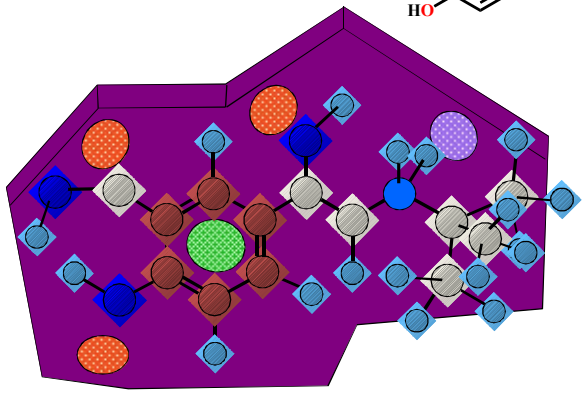




SALBUTAMOL

α-Adrenoceptor





SALBUTAMOL

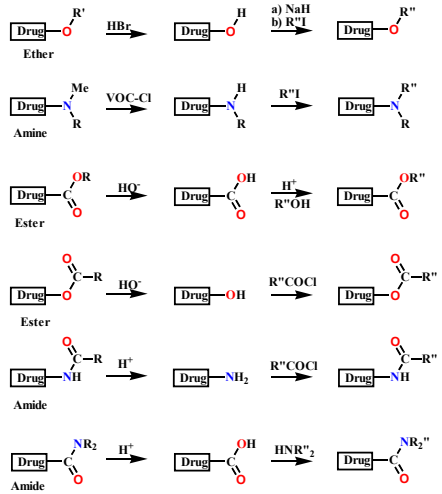
4.1 Vary Alkyl Substituents

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 *(de novo)* synthesis is usually required.

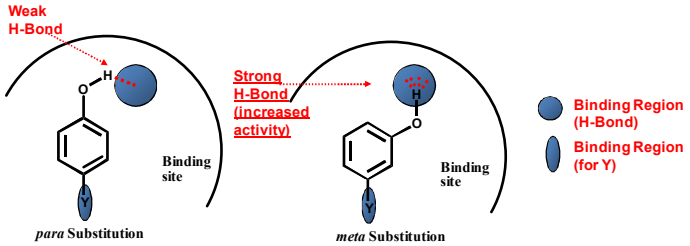
4.1 Vary Alkyl Substituents

Methods



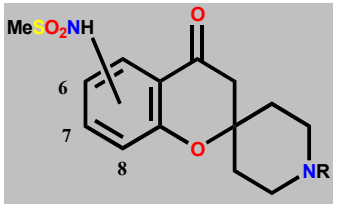
4.2 Vary Aryl Substituents

- vary substituents



4.2 Vary Aryl Substituents

Vary substitution pattern to enhance binding interactions

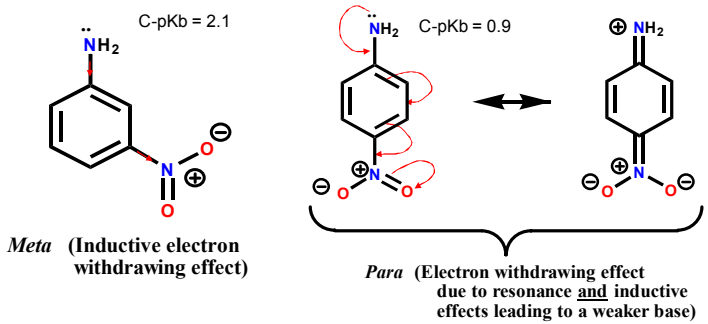


benzopyranes

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

4.2 Vary Aryl Substituents

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



Meta (Inductive electron withdrawing effect)

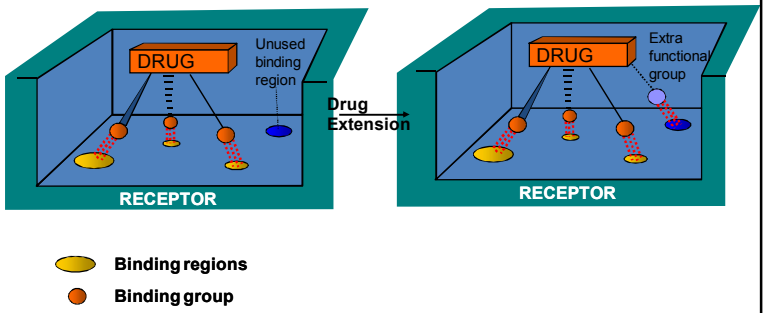
Para (Electron withdrawing effect due to resonance and inductive effects leading to a weaker base)

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

Optimalizácia štruktúry liečiva
-
pridaním funkčnej skupiny

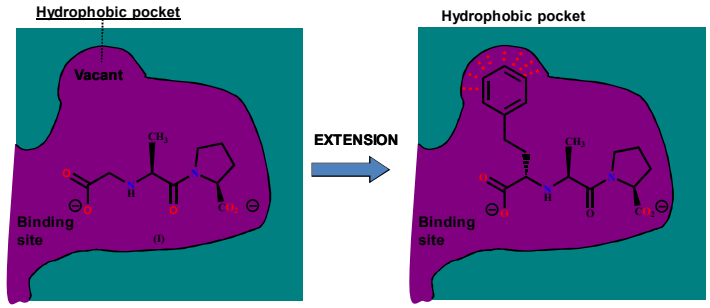
4.3 Extension - Extra Functional Groups

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



4.3 Extension - Extra Functional Groups

Example : ACE Inhibitors (& Alsheimer)

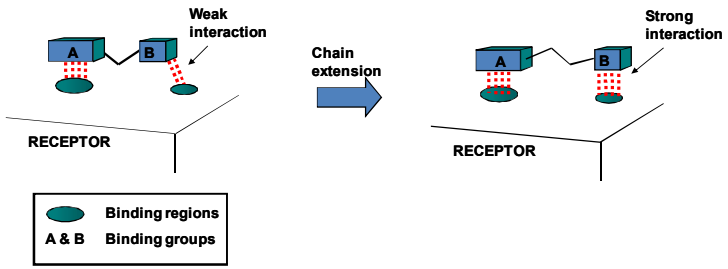


Optimalizácia štruktúry liečiva
-
zmenou veľkosti kruhu

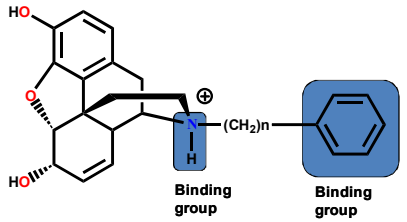
4.4 Chain Extension / Contraction

Rationale :

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

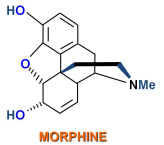


4.4 Chain Extension / Contraction



Optimum chain length = 2
***N*-Phenethylmorphine**

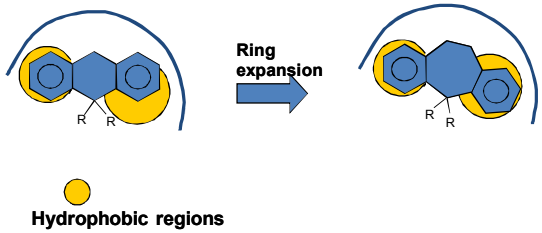
N-2-*phenetylmorphine* is about 15 times more potent than morphine itself



4.5 Ring Expansion / Contraction

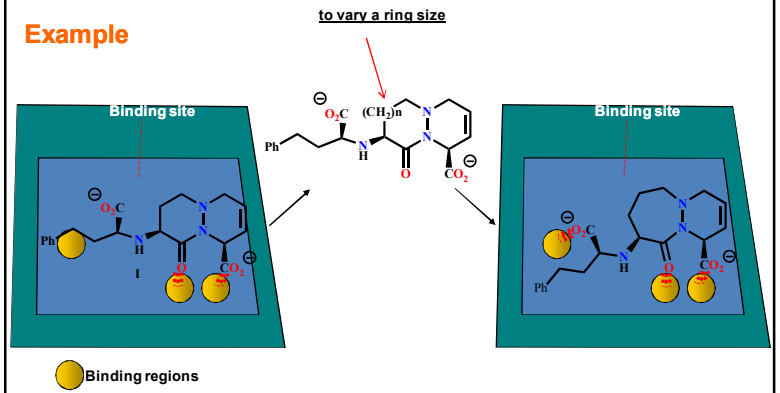
Rationale :

To improve overlap of binding groups with their binding regions



4.5 Ring Expansion / Contraction

Example



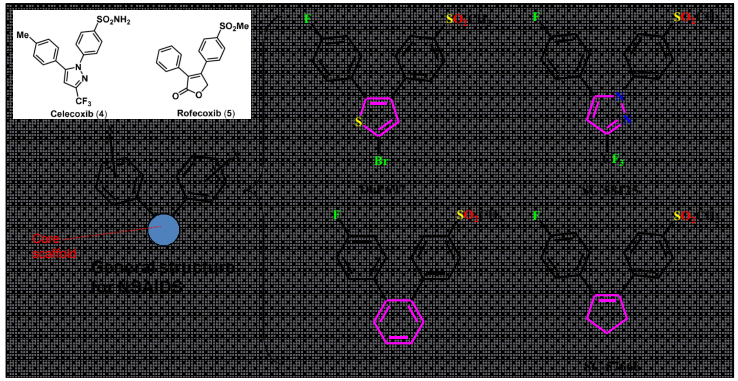
Optimalizácia štruktúry liečiva
-
zmenou charakteru kruhu

4.6 Ring Variations

Celecoxib: to treat the pain, inflammation of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation

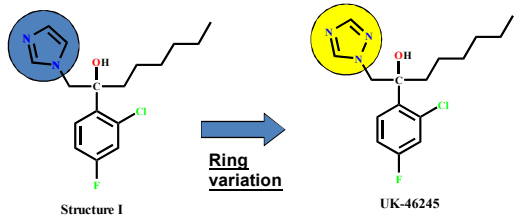
Rationale :

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



4.6 Ring Variations

sometimes results in improved properties

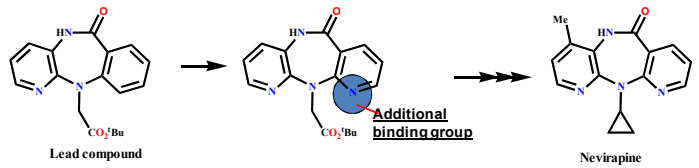


Antifungal agent

Improved selectivity against fungal enzyme

4.6 Ring Variations

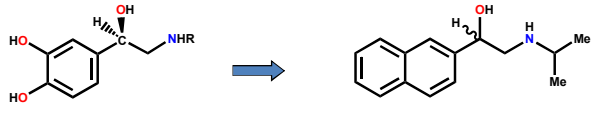
Example - Nevirapine (antiviral agent)

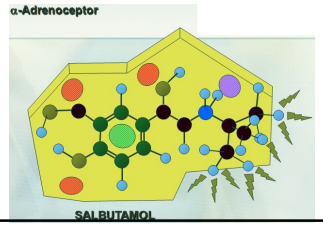


NEVIRAPINE: a non-nucleoside reverse transcriptase inhibitor (NNRTI) used **to treat HIV-1 infection** and AIDS. As with other antiretroviral drugs, HIV rapidly develops resistance if nevirapine is used alone, so recommended therapy consists of combinations of three or more antiretrovirals.

4.6 Ring Variations

Example - Pronethalol (β-blocker)





Selective for adrenergic β-receptors over α-receptors

Optimalizácia štruktúry liečiva

-

(bio)izostérnou zámenou

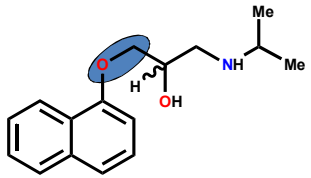
4.7 Isosteres and Bioisosteres

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 Bioisosteres

Useful for SAR



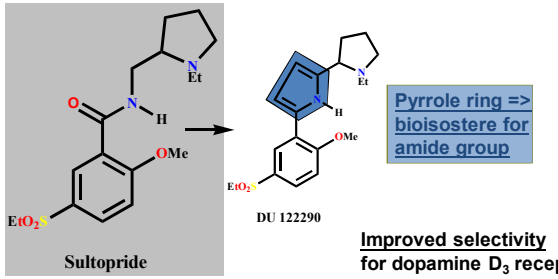
Propranolol (β-blocker)

- 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 Bioisosteres

Bioisosteres:

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



Improved selectivity for dopamine D_3 receptor over D_2 receptor

antipsychotic for the treatment of schizophrenia

Optimalizácia štruktúry liečiva
-
zjednodušením molekuly

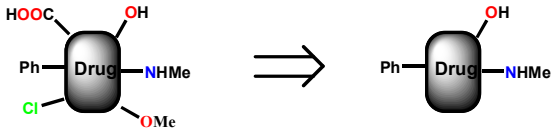
4.8 Simplification

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

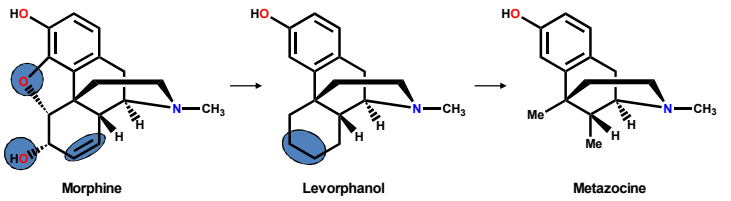
- retain pharmacophore
- remove unnecessary functional groups



4.8 Simplification

- Remove excess rings

Example

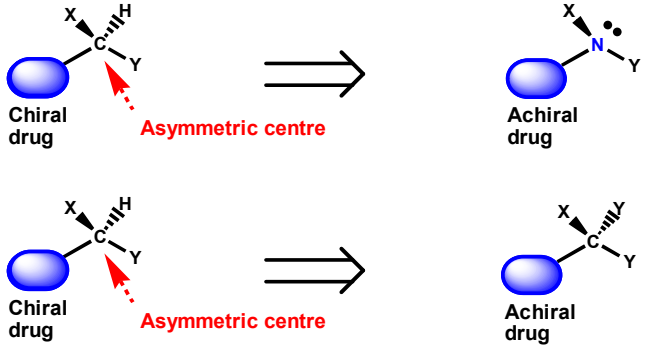


Excess functional groups Excess ring

opioid analgesic

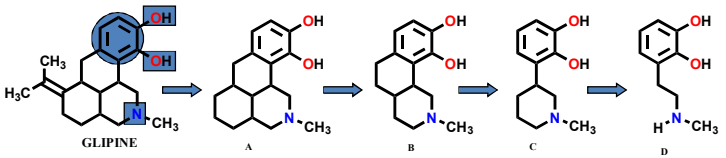
4.8 Simplification

- Remove stereogenic centres

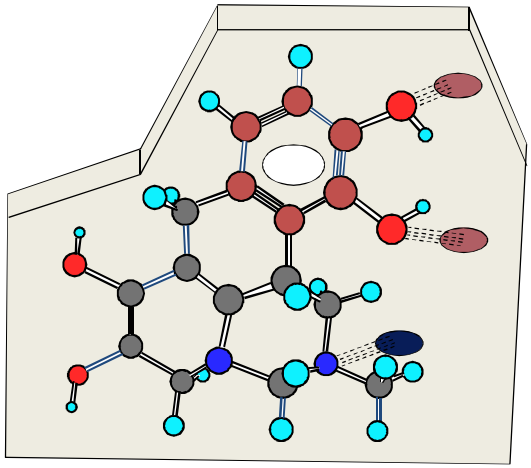


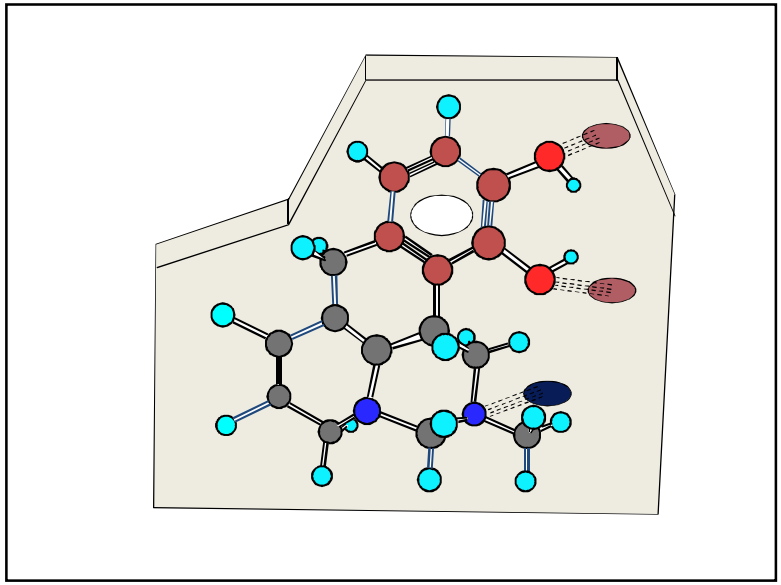
4.8 Simplification

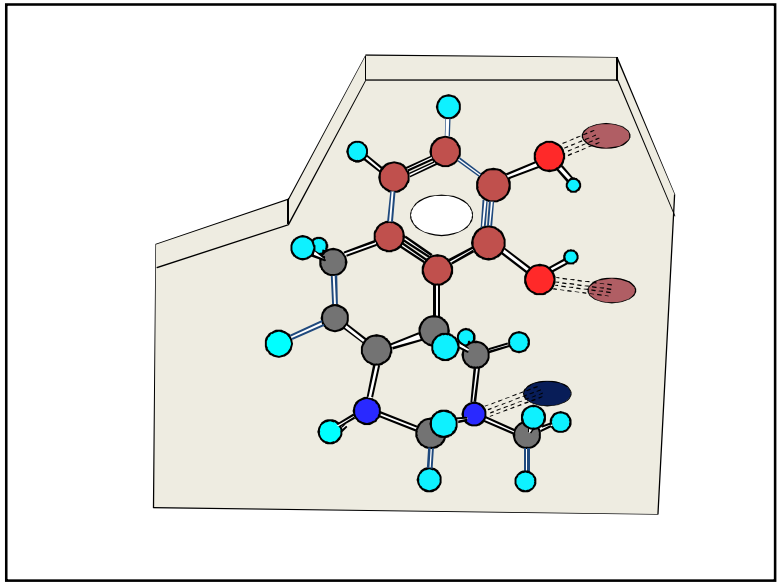
- Simplify in stages to avoid oversimplification

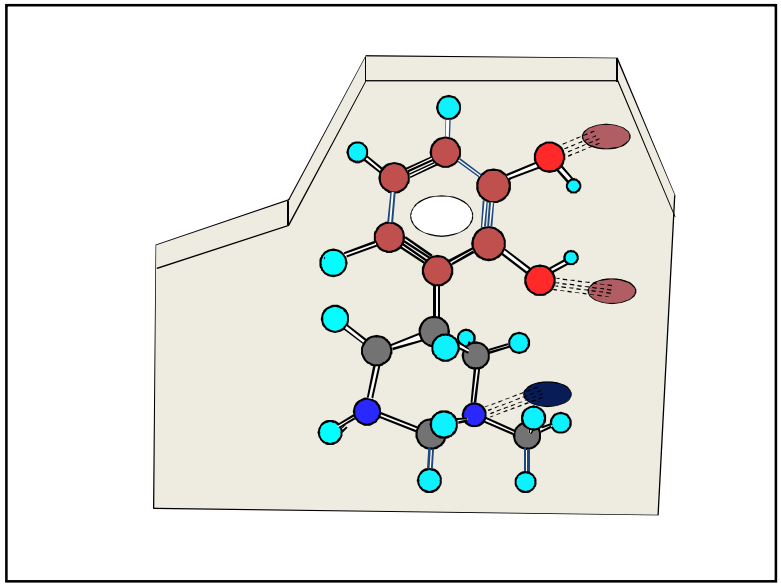


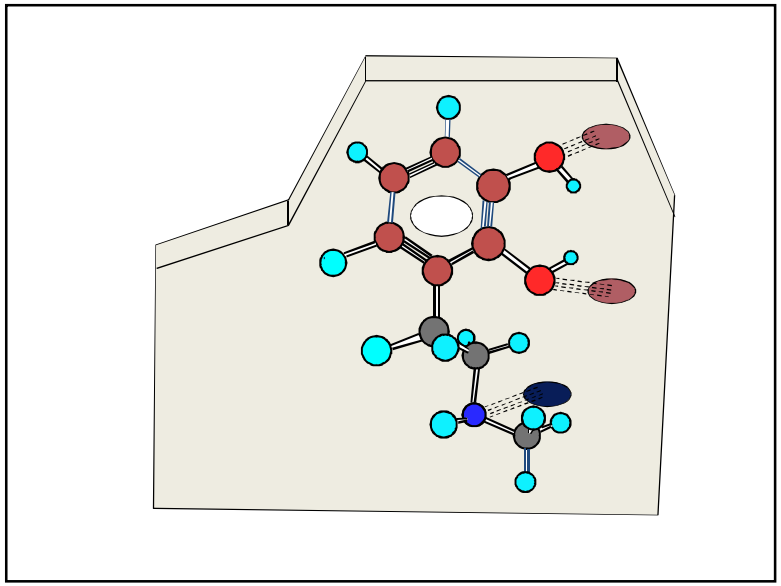
- Simplification does not mean 'pruning groups' off the lead compound
- Compounds usually made by total synthesis





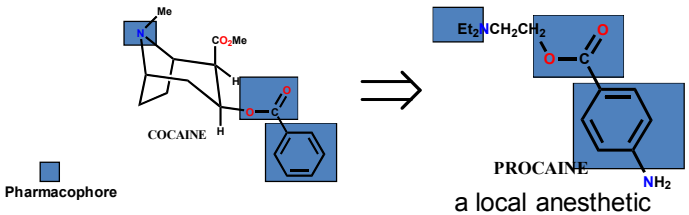






4.8 Simplification

Example



a local anesthetic

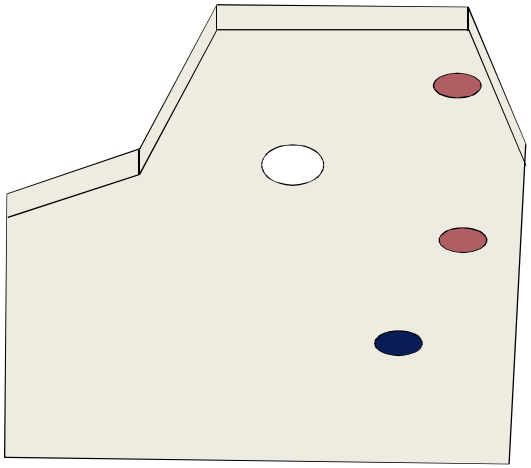
- important binding groups retained
- unnecessary ester removed
- complex ring system removed

4.8 Simplification

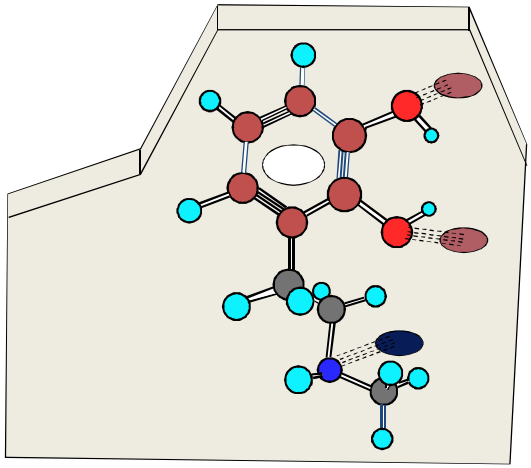
Disadvantages:

- 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*)

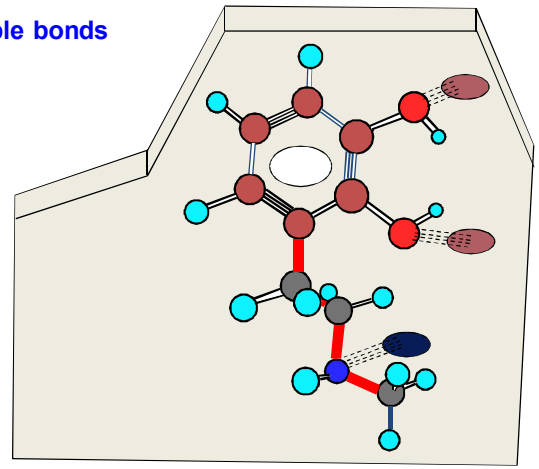


Target binding site



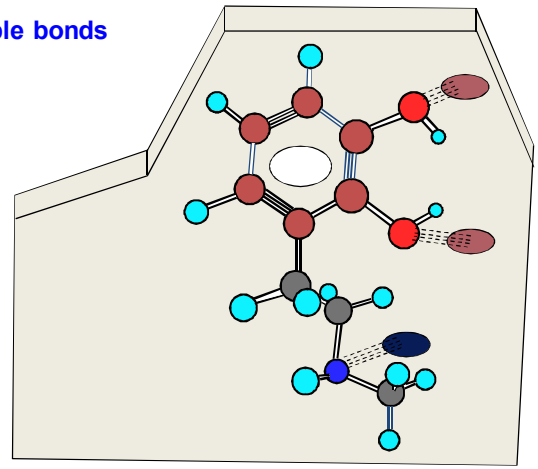
Target binding site

Rotatable bonds



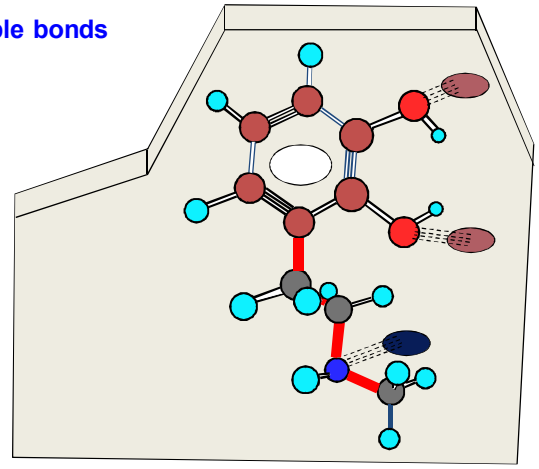
Target binding site

Rotatable bonds



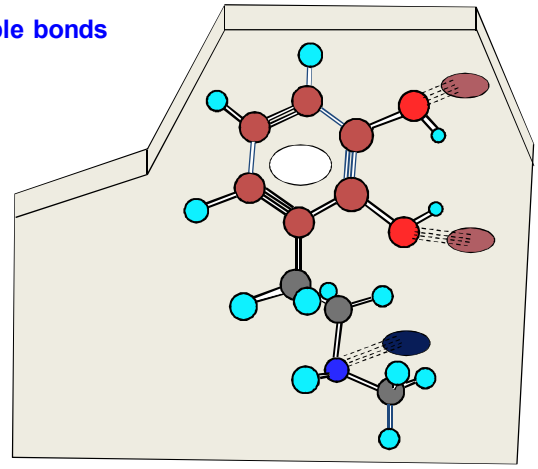
Target binding site

Rotatable bonds



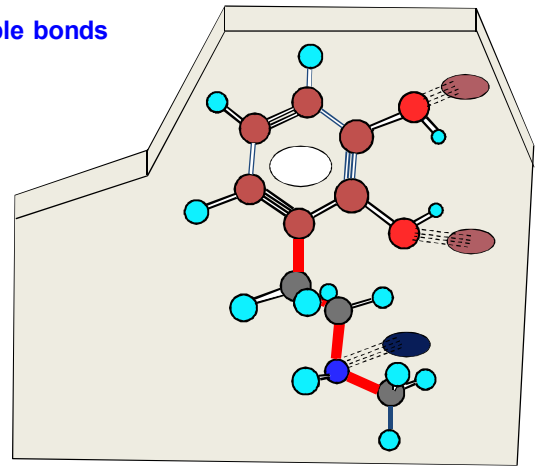
Target binding site

Rotatable bonds



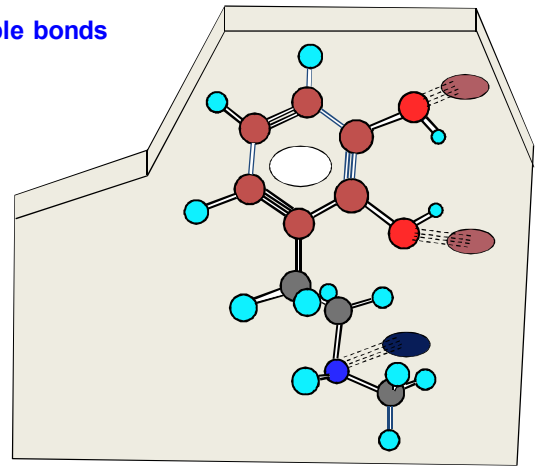
Target binding site

Rotatable bonds



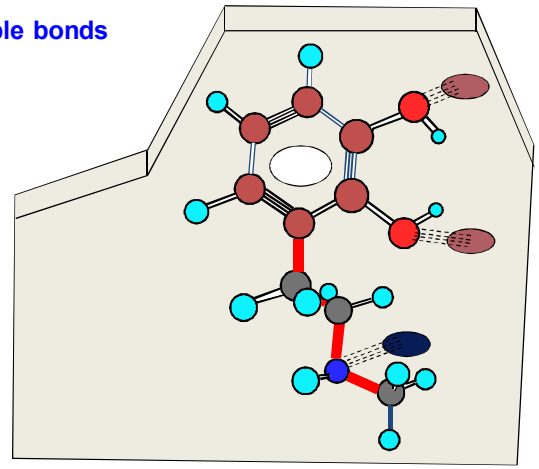
Target binding site

Rotatable bonds



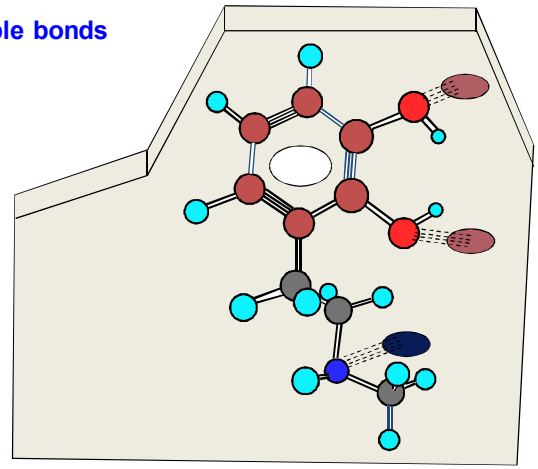
Target binding site

Rotatable bonds



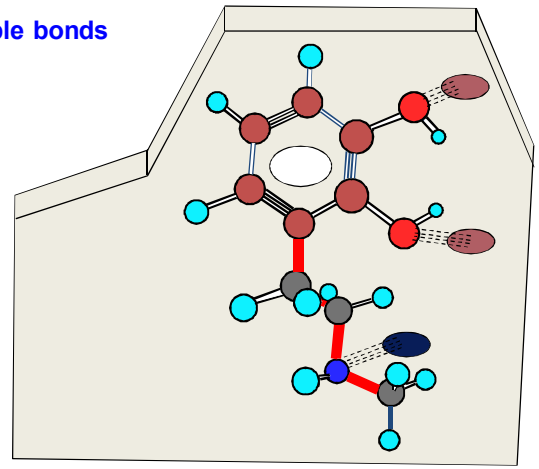
Target binding site

Rotatable bonds



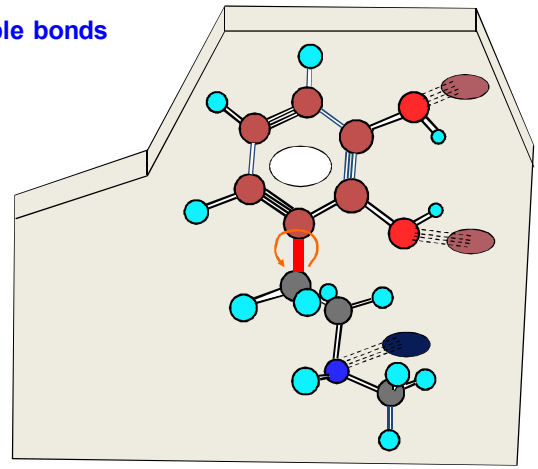
Target binding site

Rotatable bonds



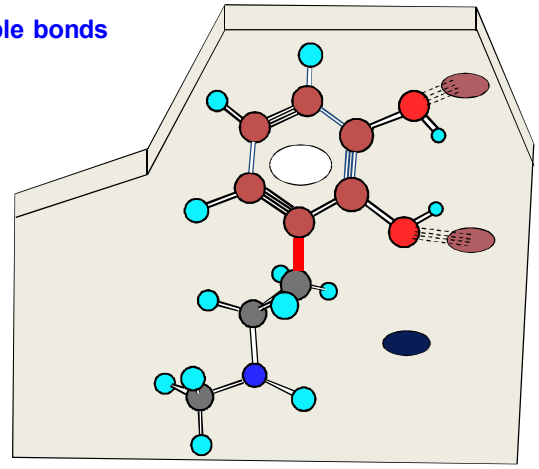
Target binding site

Rotatable bonds



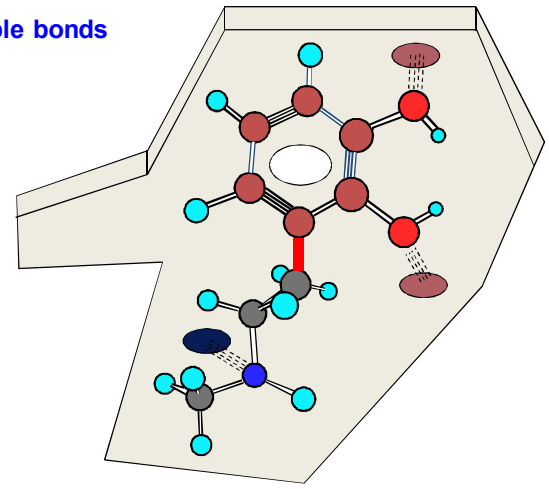
Target binding site

Rotatable bonds



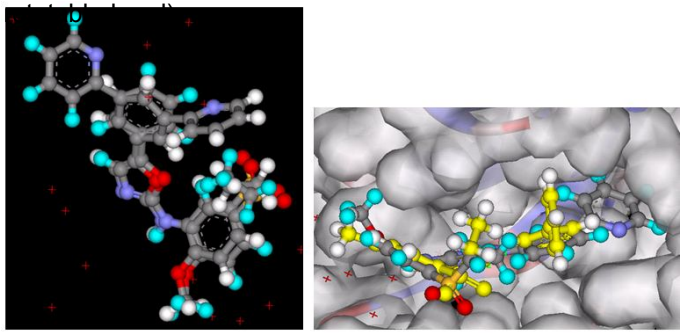
Target binding site

Rotatable bonds



Different binding site - side effects

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



1Y6A-N2,N3

Optimalizácia štruktúry liečiva - rigidifikáciou molekuly

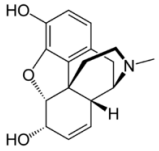
4.8 Simplification

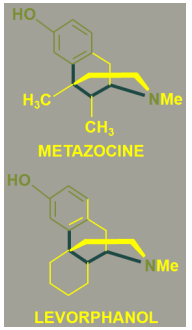
Example of oversimplification

- Simplification of opiates

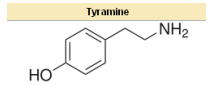
TYRAMINE is **unable to cross the blood-brain barrier**, resulting in only non-psychoactive peripheral sympathomimetic effects. A **hypertensive crisis can result**.

MORPHINE

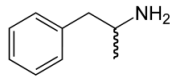




TYRAMINE

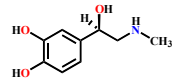


AMPHETAMINE

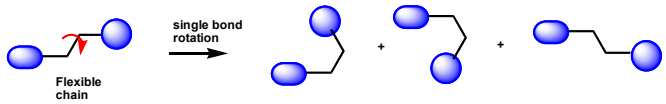


OVERSIMPLIFICATION

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)

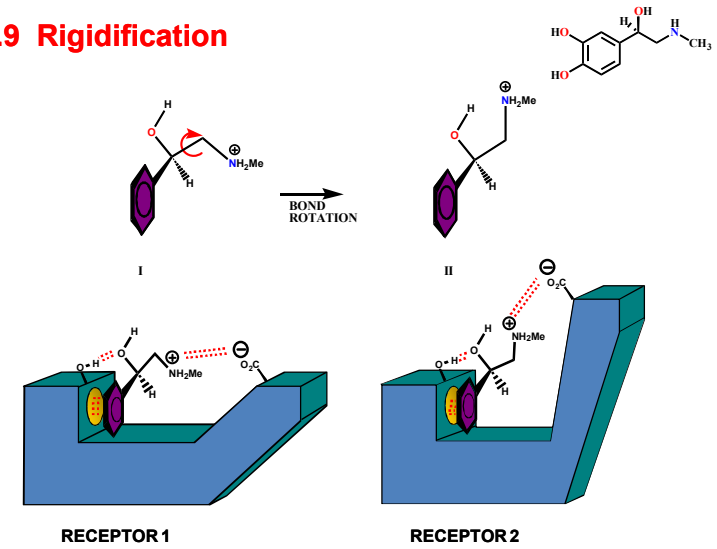


- Rigidify molecule to limit conformations => conformational restraint
  - Increases activity (more chance to be in desired active conformation)
  - Increases selectivity (less chance of undesired active conformations responsible for non selectivity)

Disadvantage:

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

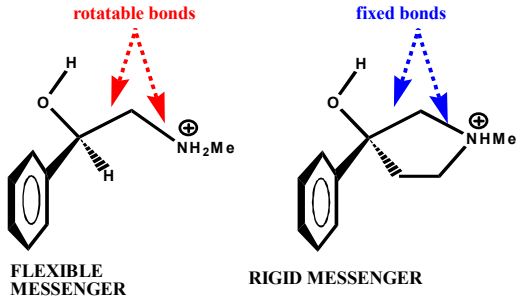
4.9 Rigidification



4.9 Rigidification

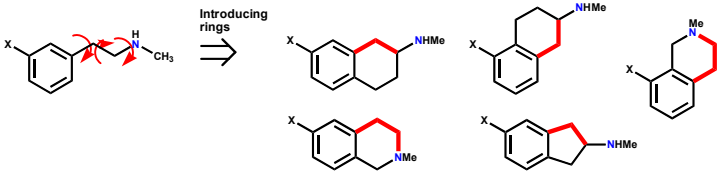
Introduce ring

bonds within ring systems are locked and cannot rotate freely



4.9 Rigidification

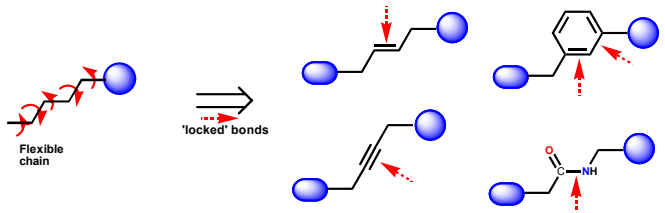
locked particular rotamers



test rigid structures to see which ones have retained active conformation

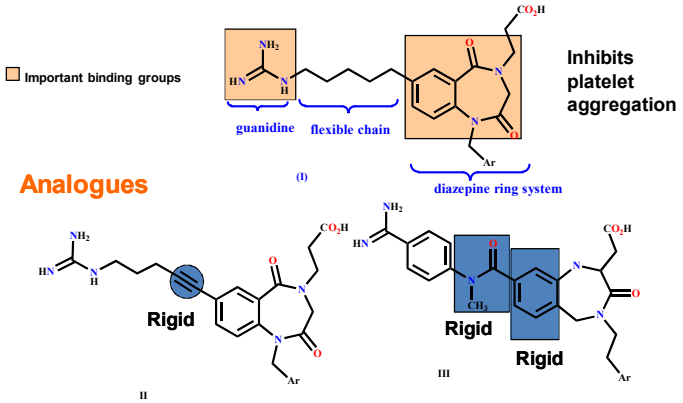
4.9 Rigidification

Introduce rigid functional groups



4.9 Rigidification

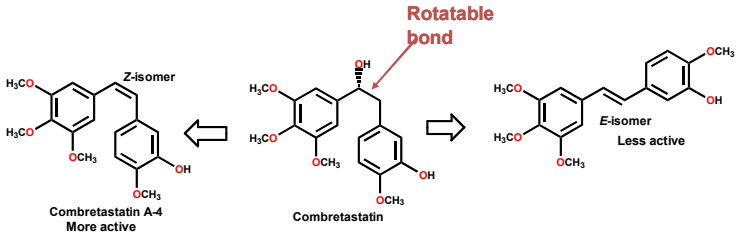
Examples



Analogues

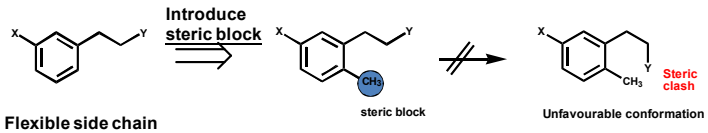
4.9 Rigidification

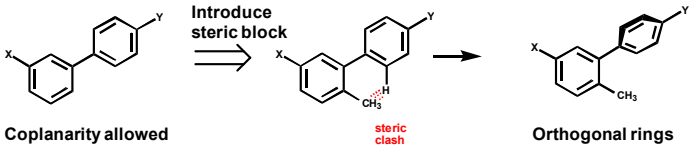
Examples - Combretastatin (anticancer agent, VDA vascular disrupting agent)



4.9 Rigidification

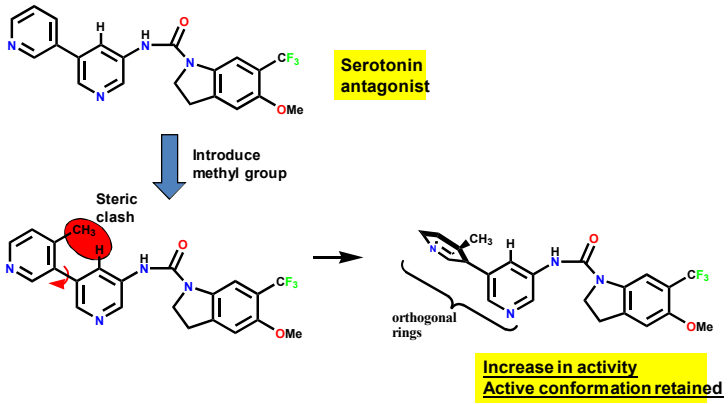
Methods - Steric Blockers





4.9 Rigidification

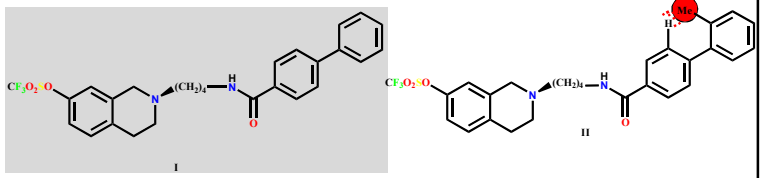
Steric Blockers - Examples



4.9 Rigidification

Steric Blockers - Examples

Steric clash



I

II

D_3 Antagonist

Inactive
Active conformation disallowed

Optimalizácia štruktúry liečiva
-
štruktúrny design

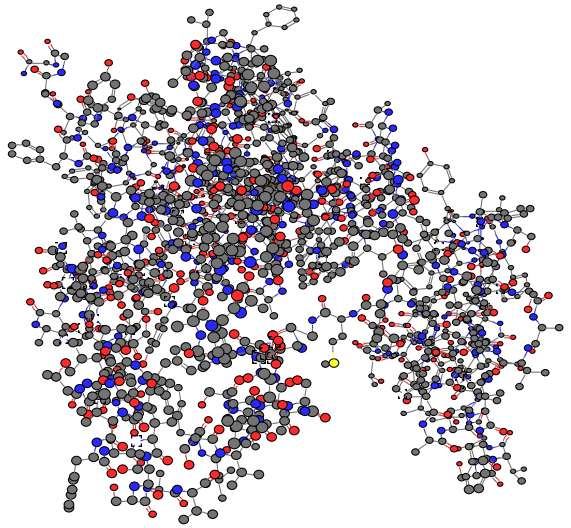
4.10 Structure based drug design

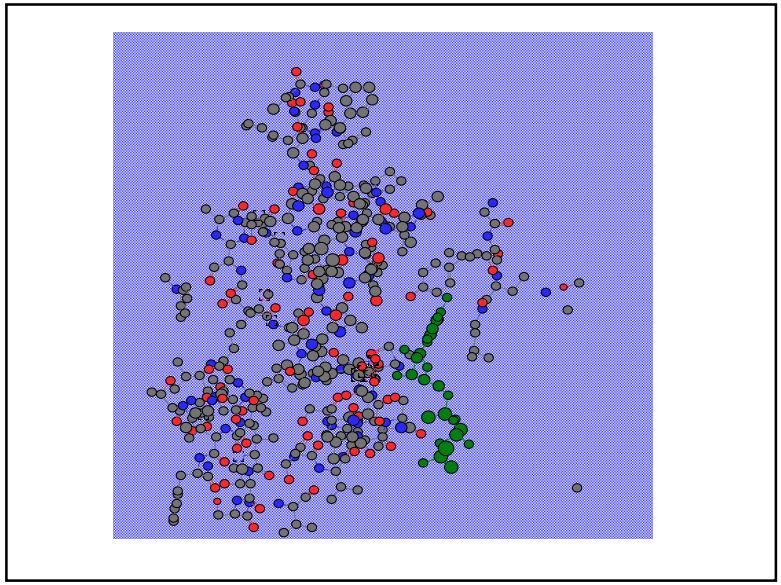
Strategy

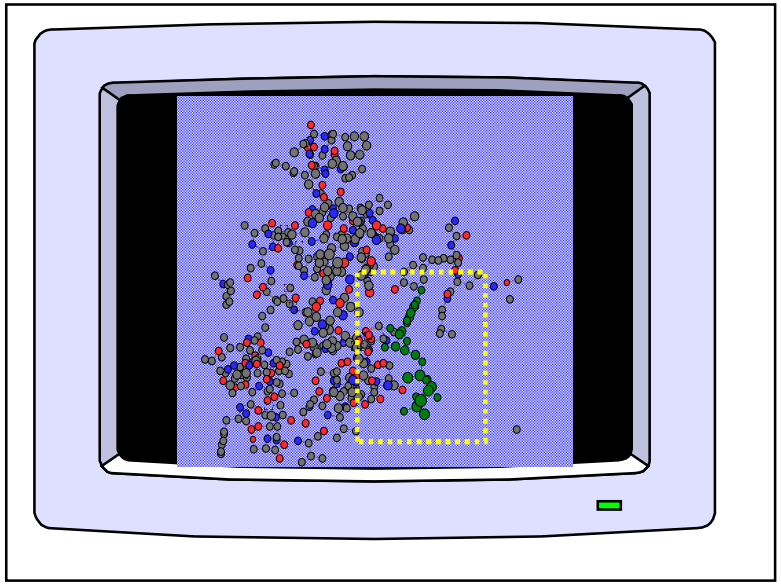
Carry out drug design based on the interactions between the lead compound and the target binding site

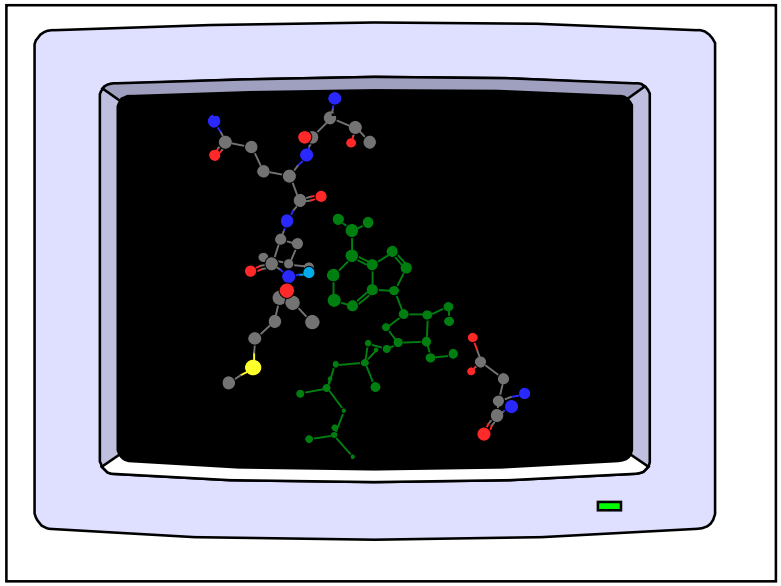
Procedure

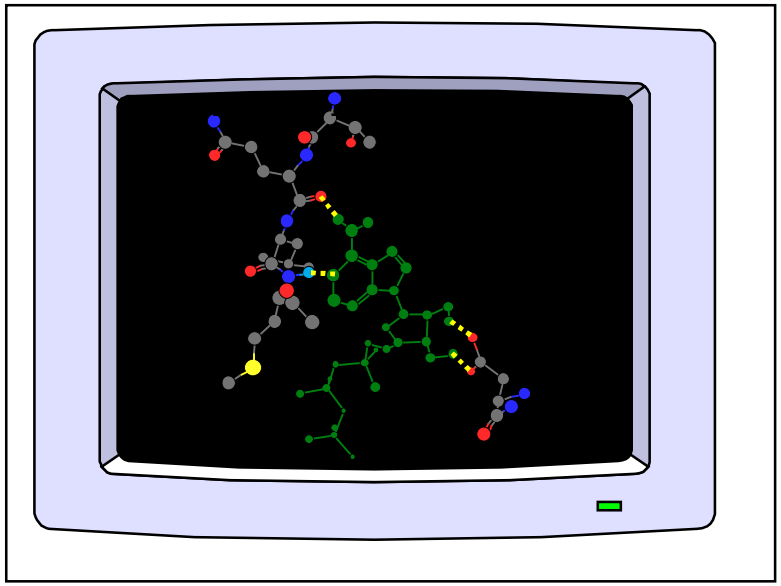
- Crystallise target protein with bound ligand (e.g. enzyme + inhibitor or ligand)
- Acquire structure by X-ray crystallography
- Identify binding site (region where ligand is bound)
- Identify binding interactions between ligand and target (modelling)
- Identify vacant regions for extra binding interactions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

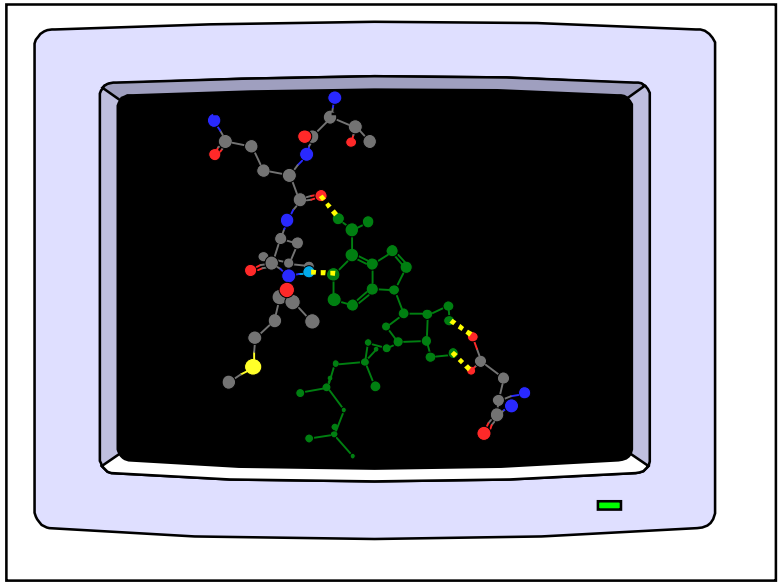


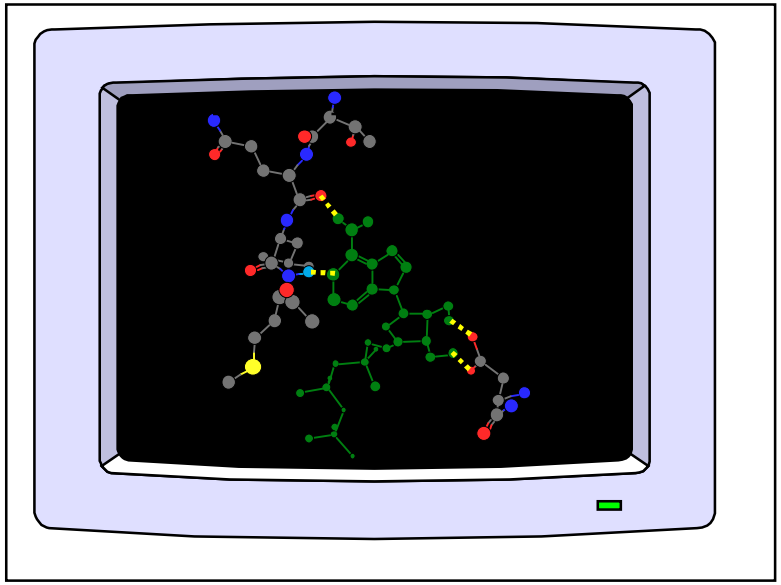


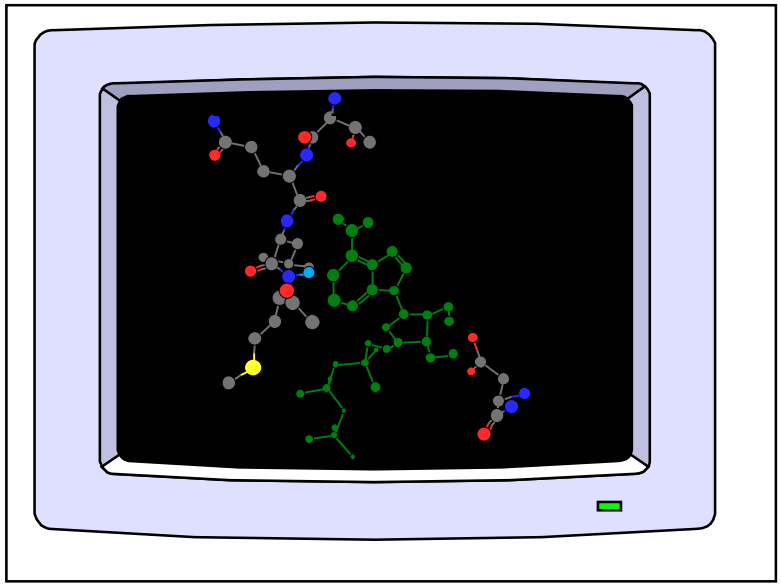


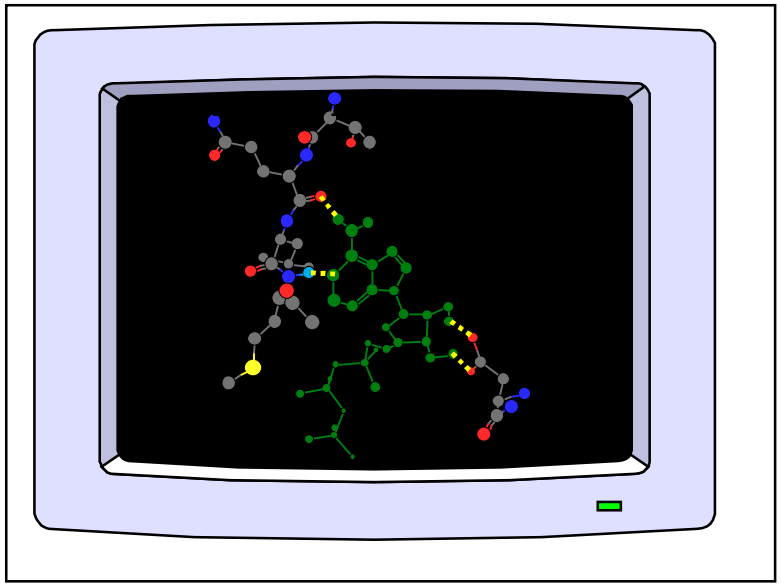


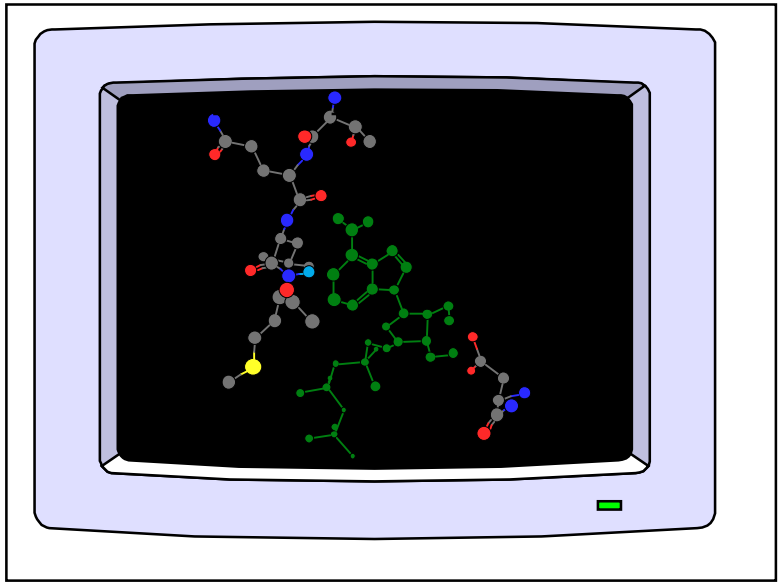


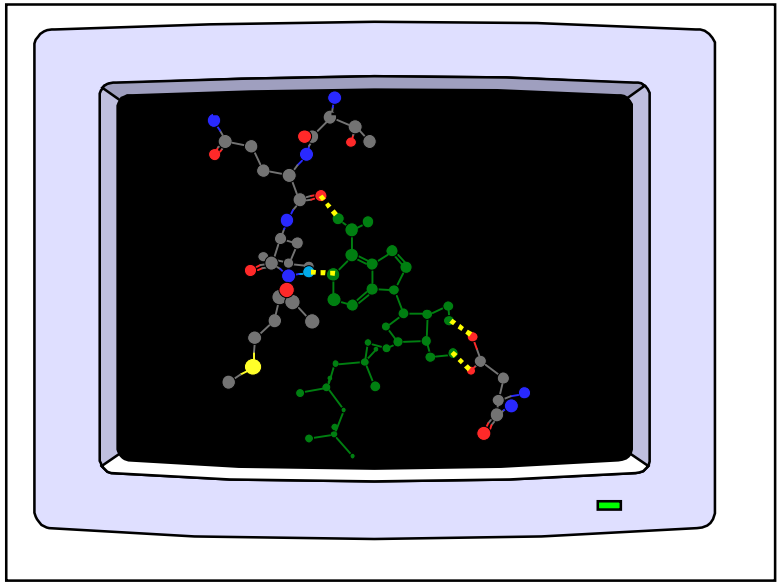


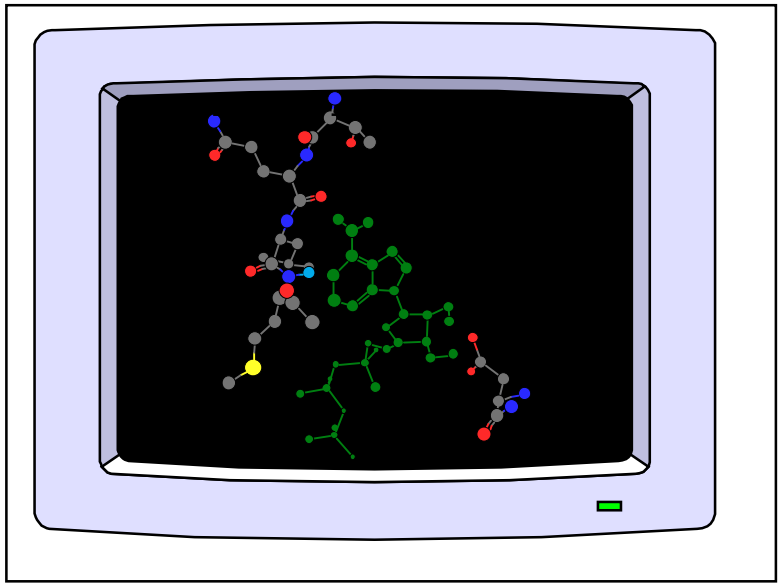


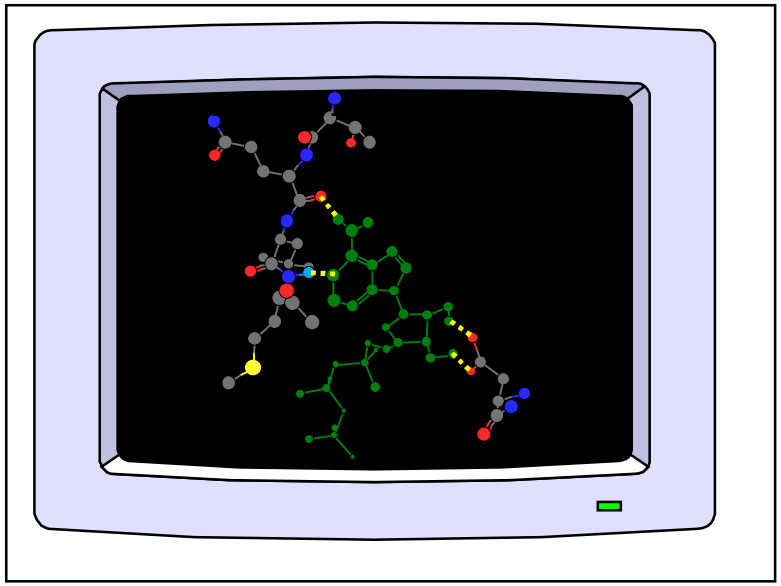


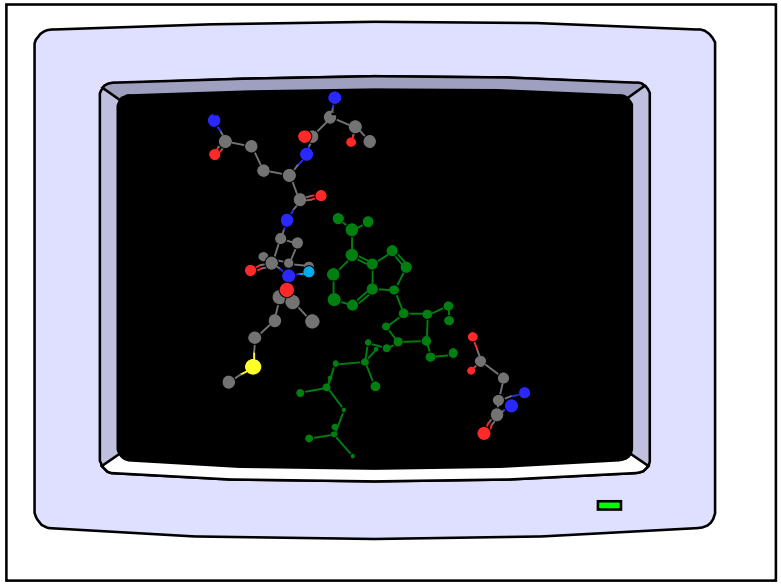


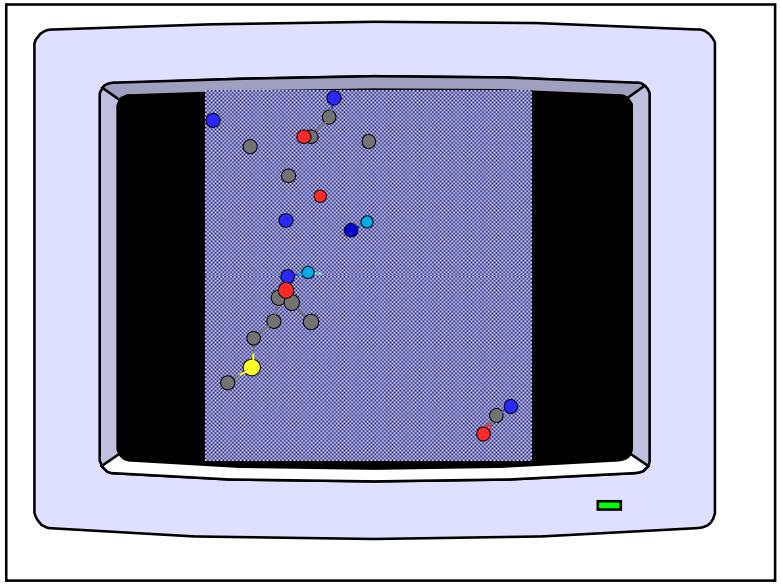






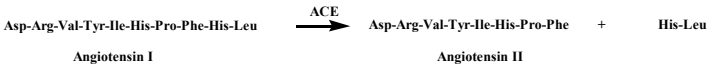






4.10 Structure based drug design

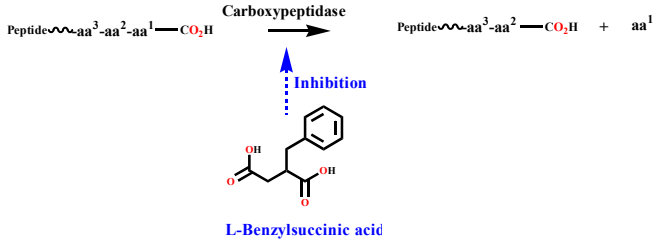
Design of Antihypertensives - ACE inhibitors



- 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

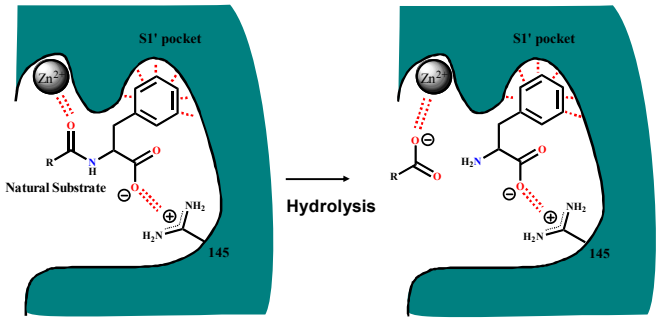
4.10 Structure based drug design

Carboxypeptidase



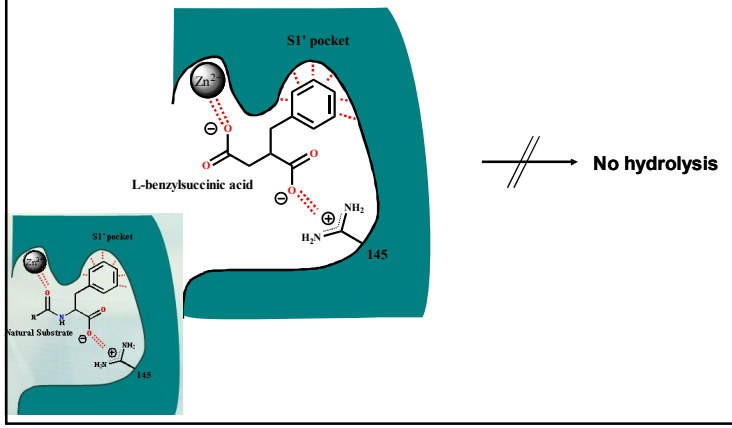
4.10 Structure based drug design

Carboxypeptidase mechanism



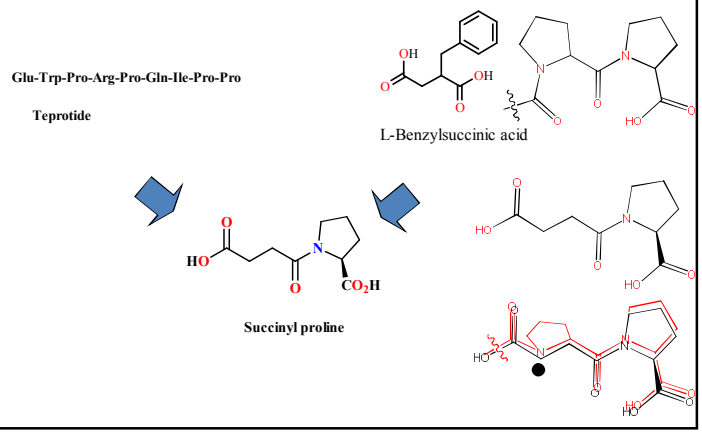
4.10 Structure based drug design

Inhibition of carboxypeptidase



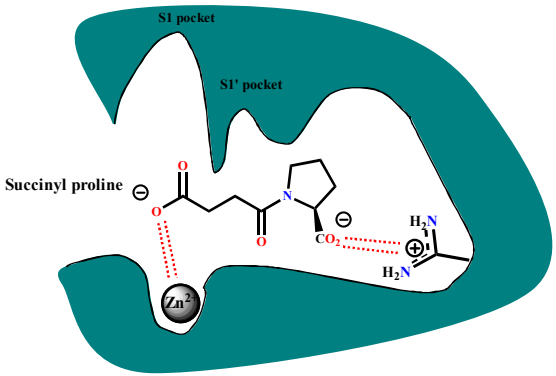
4.10 Structure based drug design

Lead compounds for ACE inhibitor



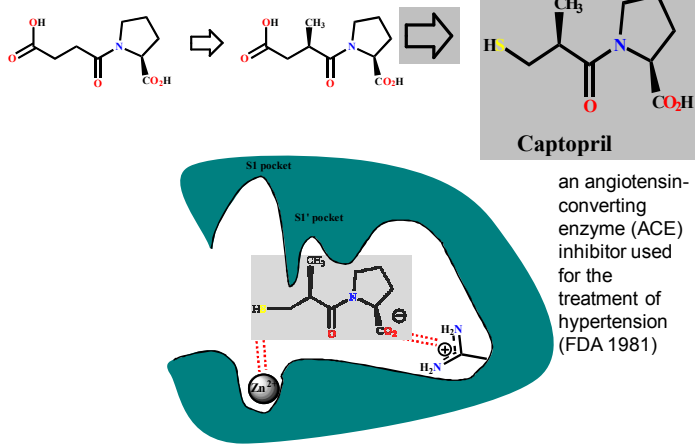
4.10 Structure based drug design

Proposed binding mode



4.10 Structure based drug design

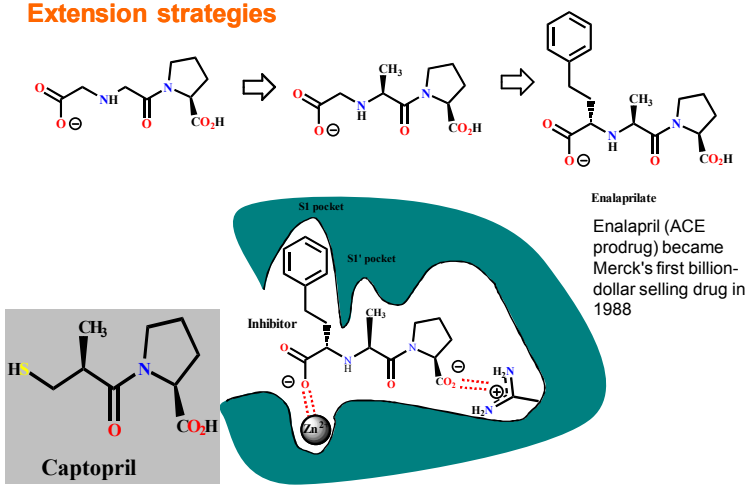
Extension and bioisostere strategies



an angiotensin-converting enzyme (ACE) inhibitor used for the treatment of hypertension (FDA 1981)

4.10 Structure based drug design

Extension strategies



Enalapril (ACE prodrug) became Merck's first billion-dollar selling drug in 1988

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