SAR

STRUCTURE - ACTIVITY RELATIONSHIPS

(alkoholy, amíny, aldehydy, ketóny, estery, amidy, kyseliny, uhľovodíky)

MCH-II Andrej Boháč

Structure Activity Relationships (SAR)

SAR - identifies which functional groups are important for binding and activity

Method

- **alter, remove or mask a functional group**
- **test the analogue for activity**

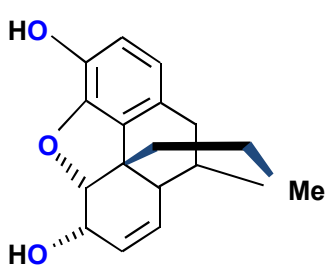
- **method of testing**
  in vitro - **for binding interactions with target (e.g. enzyme)**
  in vivo - **for target binding interactions + pharmacokinetic properties**

- **if group is removed or modified and *in vitro* activity:**
  drops or diminished => group was important for binding
  unaffected => group is not important

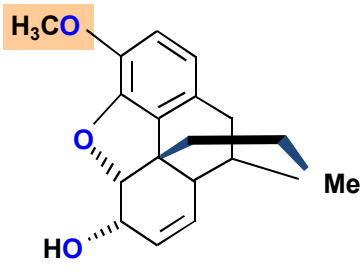
Consider by analogues:

- **modifications may disrupt binding steric or electronic effects**
- **easiest analogues are those made directly from a lead compound**
- **modifications may depend on other groups present**
- **some analogues have to be made by a full (de novo) synthesis**
  (e.g. replacing an aromatic ring with a heterocyclic ring)
- **SAR allows identification of important groups involved in binding**
- **SAR allows identification of the pharmacophore**

5. Structure Activity Relationships (SAR)

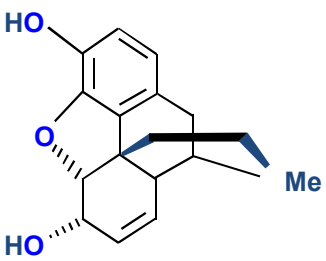


MORPHINE
an opioid analgesic drug

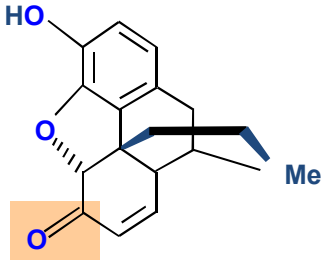


CODEINE
antitussive drug

ANALGESIC ACTIVITY DROPS



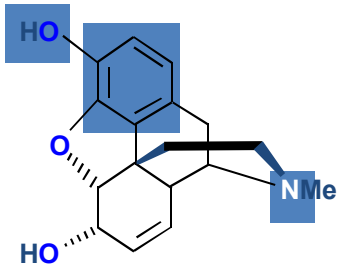
MORPHINE



6-OXYMORPHINE

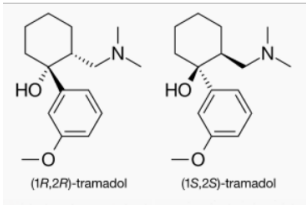
ACTIVITY UNAFFECTED

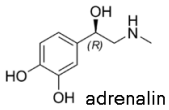
IMPORTANT GROUPS DETERMINED FOR ACTIVITY



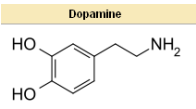
MORPHINE

Tramadol

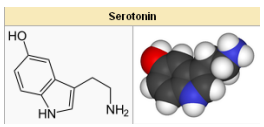




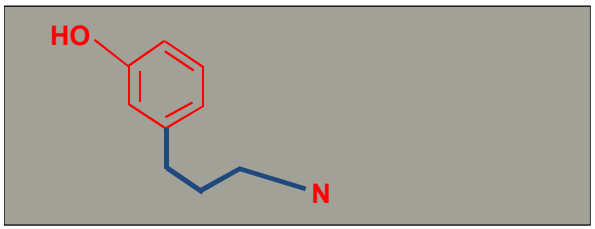
Dopamine

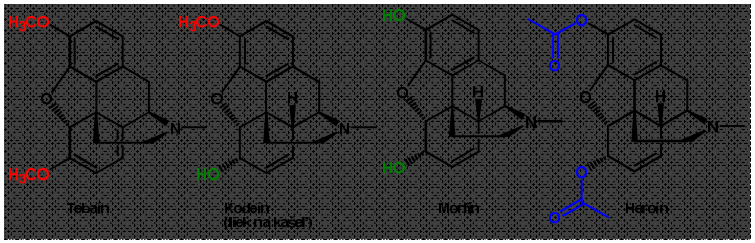


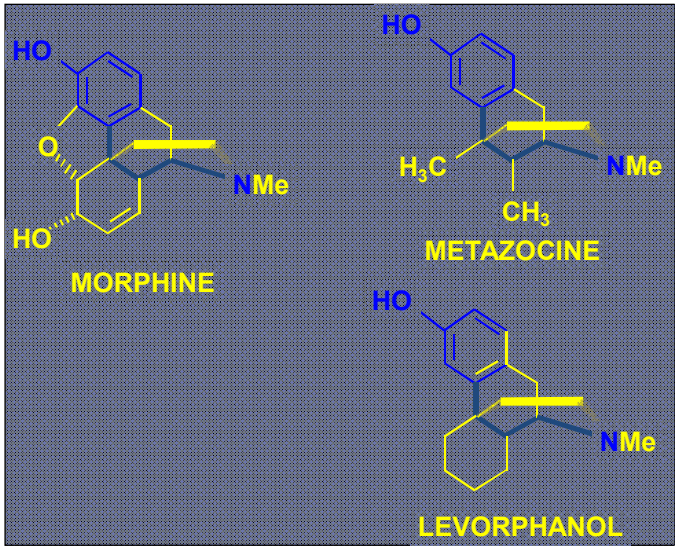
Serotonin



ANALGESIC PHARMACOPHORE FOR OPIATES

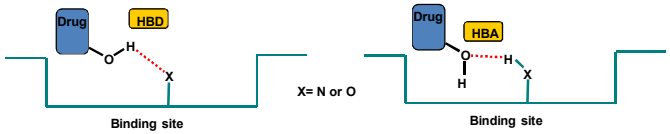




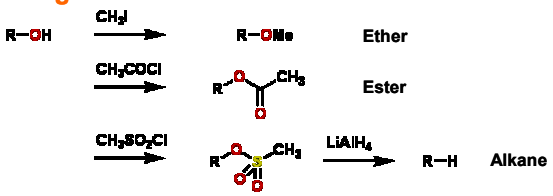


5.1 SAR on Alcohols

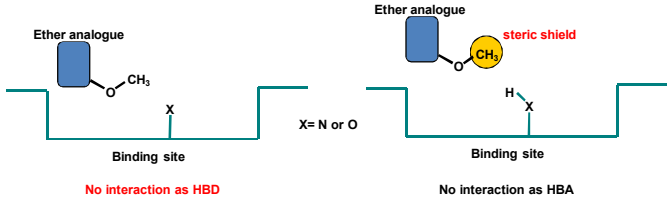
Possible binding interactions



Possible analogues



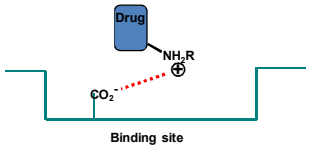
Possible effect of analogues on binding (e.g. ether)



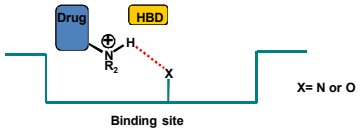
5.2 SAR on 1°, 2° & 3° Amines (RNH_2, RNHR, R_3N)

Possible binding interactions if amine is ionised

Ionic



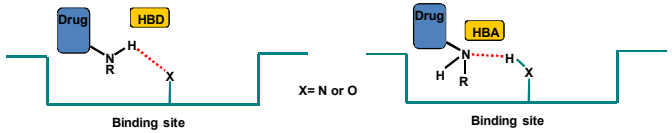
H-Bonding



$R_3\underline{N}H$ acts as a strong HBD

Possible binding interactions for free base

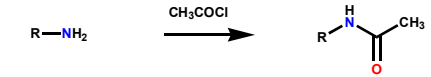
H-Bonding



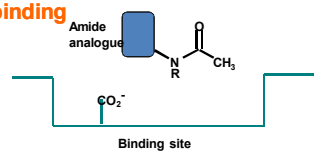
Note:

3° Amines are only able to act as HBA's - no hydrogen available to act as HBD

Analogues of 1° & 2° amines



Effect on binding

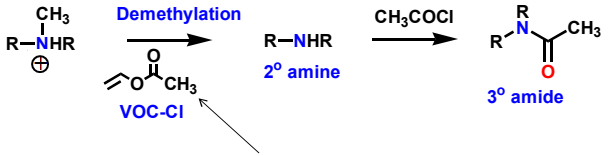


No interaction

Notes

- 1° and 2° amines are converted to 2° and 3° amides respectively
- amides cannot ionise and so ionic bonding is not possible
- an amide N is a poor HBA and so this eliminates HBA interactions
- steric effect of acyl group is likely to hinder NH acting as a HBD (2° amide)

Analogues of 3° amines containing a methyl substituent

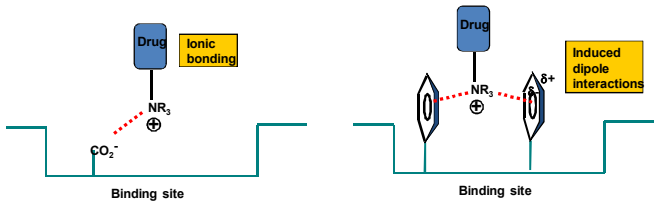


A mistake, should be a chloride

PROPOSE A MECHANISM of demetylation from nitrogen?

5.3 SAR on Quaternary Ammonium Salts (R_4N^+)

Possible binding interactions

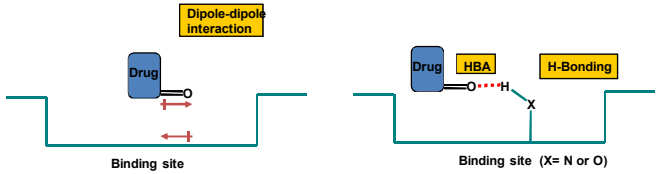


Analogues

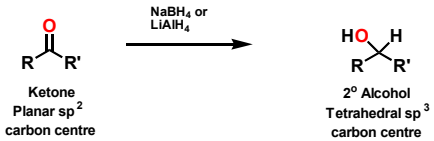
Full synthesis of 1°-2° amines and subsequently amides to disable nitrogen to form ion

5.4 SAR on Aldehydes and Ketones

Possible binding interactions



Analogues

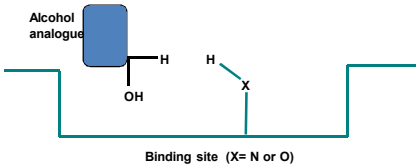


Ketone
Planar sp^2 carbon centre

2° Alcohol
Tetrahedral sp^3 carbon centre

Effect on binding

Change in stereochemistry (planar to tetrahedral)
May move oxygen out of range



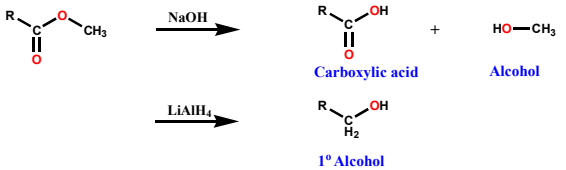
If still active, further reactions can be carried out on alcohol to establish importance of oxygen

5.5 SAR on Esters

Possible binding interactions

H-bonding as HBA by either oxygen

Analogues

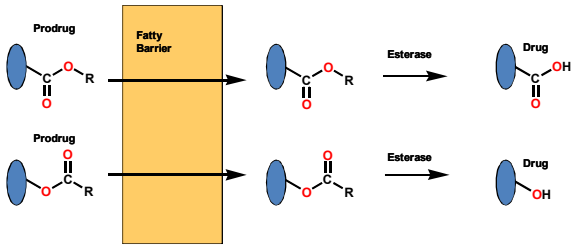


Notes

- Hydrolysis splits molecule and may lead to a loss of activity due to loss of other functional groups - only suitable for simple esters.
- Hydrolysis leads to a dramatic increase in polarity which may influence ability of analogue to reach target if *in vivo* tests are used
- Reduction to alcohol removes carbonyl group and can establish importance of the carbonyl oxygen, but reaction can be difficult to do if other labile functional groups are present

Notes

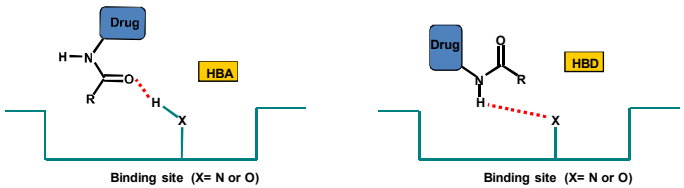
- Esters are usually hydrolysed by esterases in the blood
- Esters are more likely to be important for pharmacokinetic reasons acting as prodrugs



Ester masks polar groups
Allows passage through fatty cell membranes

5.6 SAR on Amides

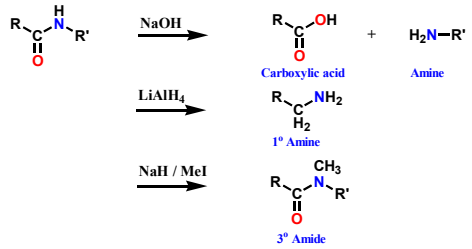
Possible binding interactions



Notes

- The nitrogen of an amide cannot act as a HBA - lone pair interacts with carbonyl group
- Tertiary amides unable to act as HBD's

Analogues

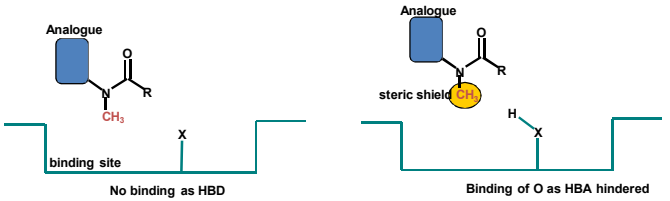


Notes

- hydrolysis splits molecule and may lead to loss of activity due to loss of other functional groups - only suitable for simple amides.
- hydrolysis leads to dramatic increase in polarity which may affect ability of analogue to reach target if *in vivo* tests are done
- reduction to amine removes carbonyl group and can establish importance of the carbonyl oxygen, but reaction may be difficult to do if other labile groups are present
- N-alkylation will disable HBD properties of NH group in 2° amides

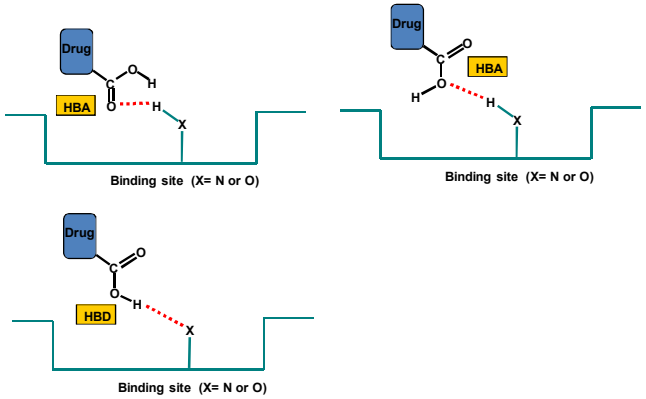
Analogues

- *N*-Methylation prevents HBD interaction and may introduce a steric effect that prevents also an HBA interaction

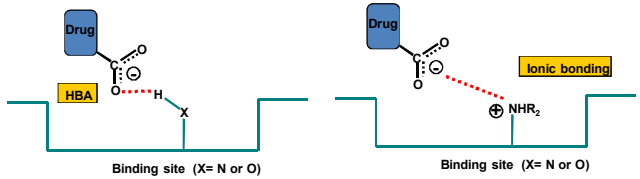


5.7 SAR on Carboxylic Acids

Possible binding interactions as free acid



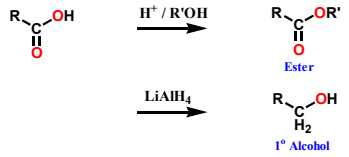
Possible binding interactions as carboxylate ion



Notes

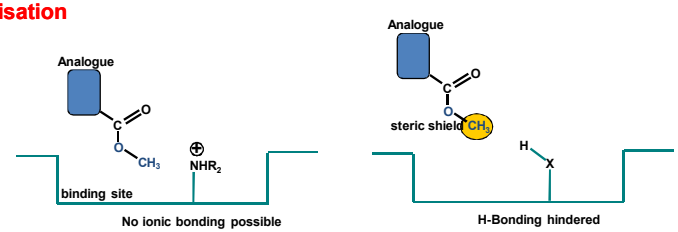
- Charged oxygen atoms are strong HBA's
- Group can interact by ionic and hydrogen bonding at the same time

Possible analogues



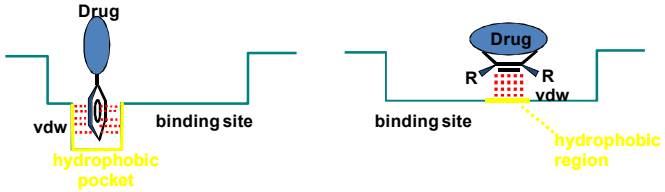
Possible effects

- **esterification prevents ionisation, HBD interactions and may hinder HBA by a steric effect**
- **reduction removes carbonyl oxygen as potential HBA and prevents ionisation**

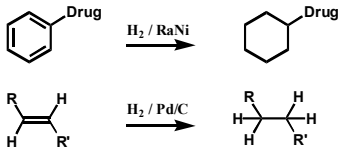


5.8 SAR on Aromatic Rings and Alkenes

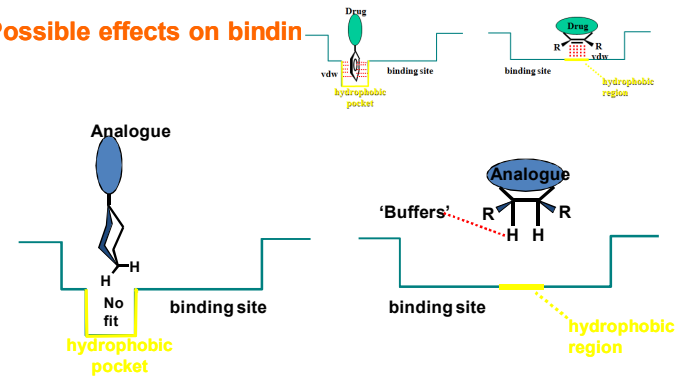
Possible binding interactions



Possible analogues

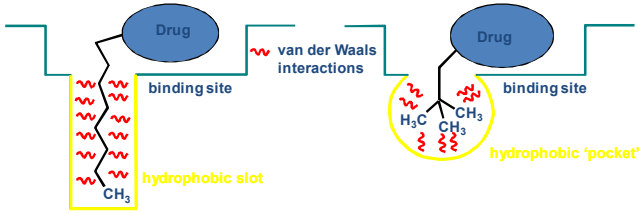


Possible effects on bindin

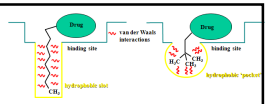


5.10 SAR of Alkyl Groups

Possible interactions



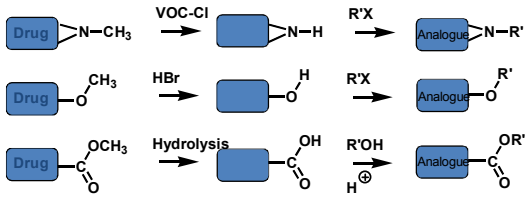
5.10 SAR of Alkyl Groups



Analogues

Easiest alkyl groups to vary are substituents on heteroatoms

Vary length and bulk of alkyl group to test space available



5.9 Miscellaneous Functional Groups in Drugs

- **acid chlorides - too reactive to be of used**
- **acid anhydrides - too reactive to be of used**
- **RX - present in anticancer drugs -react with nucleophiles in DNA**
- **ArX - commonly present. Not usually involved in binding directly (with exception of halogen bond: X....N,O bond)**
- **NO_2 - sometimes present but often toxic**
- **-C:::C- alkynes - sometimes present, but not usually important in binding interactions**
- **-SH thiols - present in some drugs as important binding group to transition metals (e.g. Zn in zinc metalloproteinases)**
- **-CN - present in some drugs but rarely involved in binding**

Notes

- **functional groups that may be important for electronic reasons (e.g. nitro, cyano, aryl halides)**
- **functional groups that may be important for steric reasons (e.g. alkynes)**