Drug Design and Discovery
Lecture 1

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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

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1. Pharmacokinetics – drug design

Aims

- **To improve pharmacokinetic properties of lead compound**
- **To optimise chemical and metabolic stability (stomach acids / digestive enzymes / metabolic enzymes)**
- **To optimise hydrophilic / hydrophobic balance (solubility in blood / solubility in GIT / solubility through cell membranes / access to CNS / excretion rate)**

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1. Pharmacokinetics – drug design

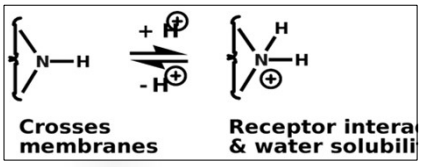
- **Drugs must be polar**

- to be soluble in aqueous conditions
- to interact with molecular targets

- **Drugs must be 'fatty'**

- to cross cell membranes
- to avoid rapid excretion

- **Drugs must have both hydrophilic and lipophilic characteristics**
- **Many drugs are weak bases with pK_a's 6-8**



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1. Pharmacokinetics – drug design

1.1 Solubility and membrane permeability

1.2 Drug stability

1.3 Drug targeting

1.4 Reducing drug toxicity

1.5 Prodrugs

1.6 drug Sunergy

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1.1 Solubility and membrane permeability

1.1.1. Vary alkyl substituents

1.1.2. 'Masking' or removing polar groups

1.1.3. Adding polar groups

1.1.4. Vary pK_a

1.1.5. Bioisosteric replacement

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1.1 Solubility and membrane permeability

1.1.1 Vary alkyl substituents

Rationale:

- **Varying the size of alkyl groups varies the hydrophilic / hydrophobic balance of the structure**
- **Larger alkyl groups increase hydrophobicity**

Disadvantage:

- **May interfere with target binding for steric reasons**

Methods:

- **Often feasible to remove alkyl groups from heteroatoms and replace with different alkyl groups**
- **Usually difficult to remove alkyl groups from the carbon skeleton ?????**

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1.1.2 'Masking' or removing polar groups

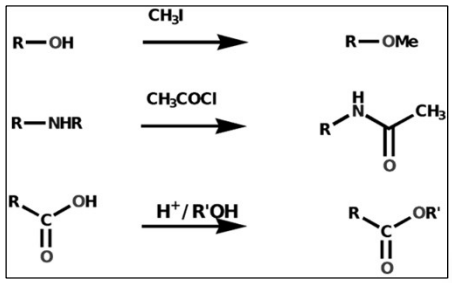
Rationale:

- **Masking or removing polar groups decreases polarity and increases hydrophobic character**

Disadvantages:

- **Polar group may be involved in target binding**
- **Unnecessary polar groups are likely to have been removed already (simplification strategy)**
- **See also prodrugs**

Methods:



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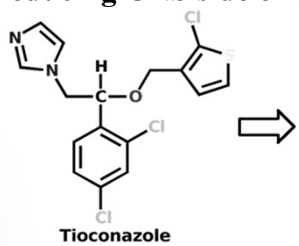
1.1.3 Adding polar groups

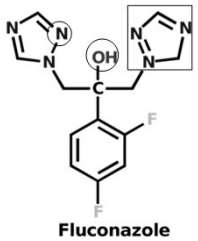
Rationale:

- **Adding polar groups increases polarity and decreases hydrophobic character**
- **Useful for targeting drugs vs. gut infections**
- **Useful for reducing CNS side effects**



Tioconazole

Antifungal agent with poor solubility - skin infections only



Fluconazole

Systemic antifungal agent improved blood solubility

Disadvantage:

- **May introduce unwanted side effects**

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1.1.4 Vary pK_a

Rationale:

- **Varying pK_a alters percentage of drug which is ionized**
- **Alter pK_a to obtain required ratio of ionized to unionized drug**

Method:

- **Vary alkyl substituents on amine nitrogens**
- **Vary aryl substituents to influence aromatic amines or aromatic carboxylic acids**

Disadvantage:

- **May affect binding interactions**

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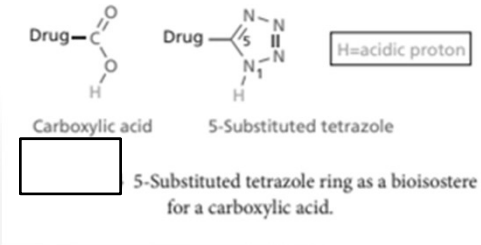
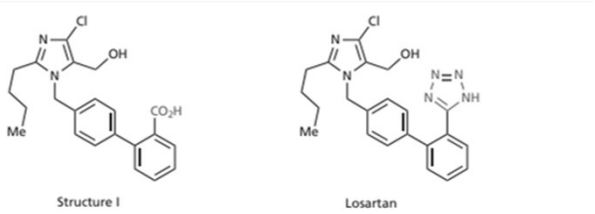
1.1.5. Bioisosteric replacement



5-Substituted tetrazole ring as a bioisostere for a carboxylic acid.



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1.2 Drug stability

- 1.2.1 Steric Shields
- 1.2.2 'Electronic shielding' of NH_2
- 1.2.3 Stereoelectronic Effects
- 1.2.4 Bio-isosteres
- 1.2.5 Metabolic blockers
- 1.2.6 Remove / replace susceptible metabolic groups
- 1.2.7 Shifting susceptible metabolic groups
- 1.2.8 Introducing susceptible metabolic groups

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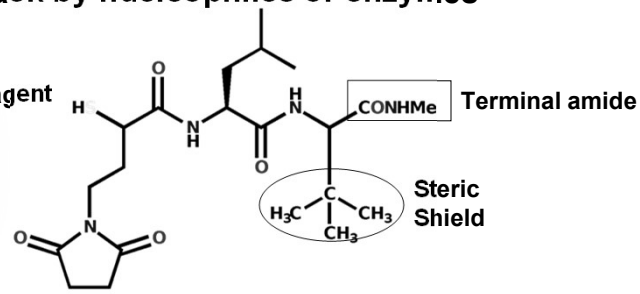
1.2 Drug stability

1.2.1 Steric Shields

Rationale:

- **Used to increase chemical and metabolic stability**
- **Introduce bulky group as a shield**
- **Protects a susceptible functional group (e.g. ester) from hydrolysis**
- **Hinders attack by nucleophiles or enzymes**

Antirheumatic agent D1927



Blocks hydrolysis of terminal amide

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1.2.2 'Electronic shielding' of NH_2

Rationale:

- **Used to stabilise labile functional groups (e.g. esters)**
- **Replace labile ester with more stable urethane or amide**
- **Nitrogen feeds electrons into carbonyl group and makes it less reactive**
- **Increases chemical and metabolic stability**

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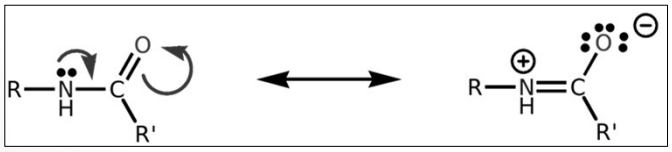
1.2.2 'Electronic shielding' of NH_2



Amides are more resistant to chemical hydrolysis, due to the lone pair of the nitrogen feeding its electrons into the carbonyl group and making it less electrophilic

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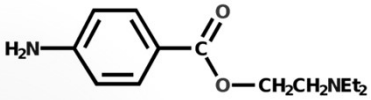
1.2.3 Stereoelectronic Effects

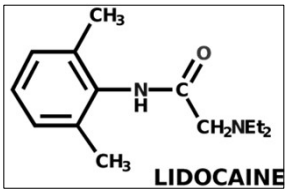
Rationale:

- **Steric and electronic effects used in combination**
- **Increases chemical and metabolic stability**



PROCAINE

Local anaesthetic (short duration)



LIDOCAINE

***ortho* Methyl groups act as steric shields & hinder hydrolysis by esterases**
Amide more stable than ester (electronic effect)

See also: oxacillin and bethanechol

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1.2.4 Bio-isosteres

Rationale:

- **Replace susceptible group with a different group without affecting activity**
- **Bio-isostere shows improved pharmacokinetic properties**
- **Bio-isosteres are not necessarily isosteres**

Examples:

- **Amides and urethanes for esters (see earlier)**
- **Du122290 (dopamine antagonist)**

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1.2.5 Metabolic blockers

Rationale:

- **Metabolism of drugs usually occur at specific sites. Introduce groups at a susceptible site to block the reaction**
- **Increases metabolic stability and drug lifetime**

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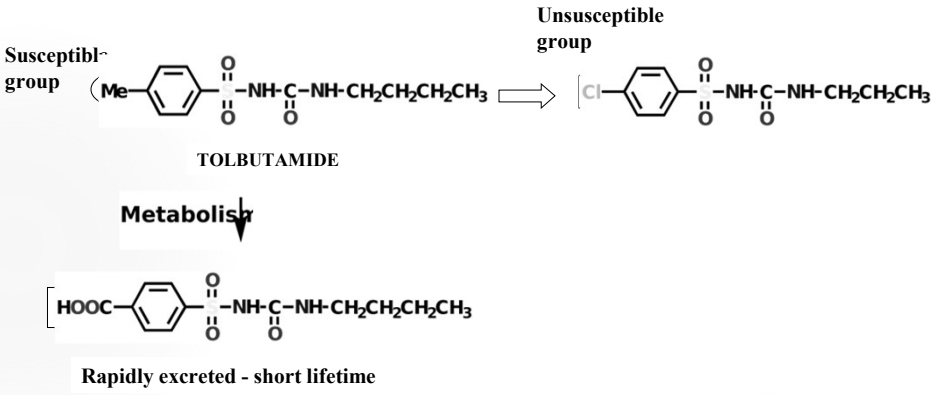
1.2.6 Remove / replace susceptible metabolic groups

Rationale:

- **Metabolism of drugs usually occurs at specific groups.**
- **Remove susceptible group or replace it with metabolically stable group [e.g. modification of tolbutamide]**



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1.2.7 Shifting susceptible metabolic groups

Rationale:

- **Used if the metabolically susceptible group is important for binding**
- **Shift its position to make it unrecognisable to metabolic enzyme**
- **Must still be recognisable to target**

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1.2 Drug stability

- 1.2.1 Steric Shields
- 1.2.2 'Electronic shielding' of NH_2
- 1.2.3 Stereoelectronic Effects
- 1.2.4 Bio-isosteres
- 1.2.5 Metabolic blockers
- 1.2.6 Remove / replace susceptible metabolic groups
- 1.2.7 Shifting susceptible metabolic groups
- 1.2.8 Introducing susceptible metabolic groups

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1.2.8 Introducing susceptible metabolic groups

Rationale:

- **Used to decrease metabolic stability and drug lifetime**
- **Used for drugs which 'linger' too long in the body and cause side effects**
- **Add groups known to be susceptible to Phase I or Phase II metabolic reactions**

Example:

Anti-arthritic agents

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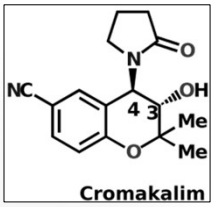
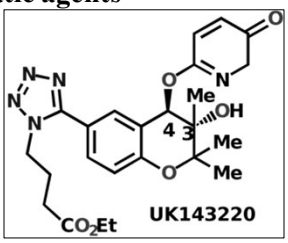
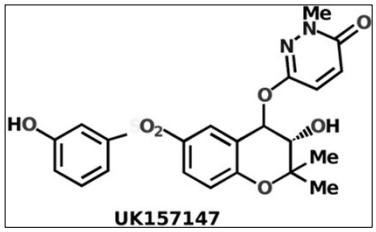
1.2.8 Introducing susceptible metabolic groups

Example:

Anti-asthmatic agents







- **Cromakalim produces cardiovascular side effects if it reaches blood supply**
- **Add metabolic instability such that compound rapidly metabolised in blood**
- **UK143220 - ester quickly hydrolysed by esterases to inactive acid**
- **UK 157147- phenol quickly conjugated and eliminated**

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Introducing chemically susceptible groups

Rationale

- **Used to decrease drug lifetime**
- **Avoids reliance on metabolic enzymes and individual variations**

Example Atracurium - i.v. neuromuscular blocking agent

- **Stable at acid pH, unstable at blood pH (slightly alkaline)**
- **Self destructs by Hoffmann elimination and has short lifetime**
- **Allows anaesthetist to control dose levels accurately**
- **Quick recovery times after surgery**

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1.3 Drug targeting

1.3.1 Linking a biosynthetic building block

1.3.2 Linking drugs to monoclonal antibodies

1.3.3 Targeting gut infections

1.3.4 Targeting peripheral regions over CNS

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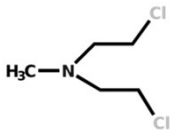
1.3 Drug targeting

1.3.1 Linking a biosynthetic building block

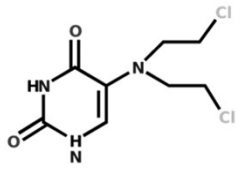
Rationale:

- **Drug 'smuggled' into cell by carrier proteins for natural building block (e.g. amino acids or nucleic acid bases)**
- **Increases selectivity of drugs to target cells and reduces toxicity to other cells**

Example:
Anticancer drugs



Non selective alkylating agent
Toxic



Uracil Mustard

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1.3.2 Linking drugs to monoclonal antibodies

Example:

Anticancer agents

Rationale:

- **Identify an antigen which is overexpressed on a cancer cell**
- **Clone a monoclonal antibody for the antigen**
- **Attach a drug or poison (e.g. ricin) to the monoclonal antibody**
- **Antibody carries the drug to the cancer cell**
- **Drug is released at the cancer cell**

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1.3.3 Targeting gut infections

Rationale:

- **Design the antibacterial agent to be highly polar or ionised**
- **Agent will be too polar to cross the gut wall**
- **Agent will be concentrated at the site of infection**
- **Example - highly ionised sulfonamides**

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1.3.4 Targeting peripheral regions over CNS

Rationale

- **Increase polarity of the drug**
- **Drug is less likely to cross the blood brain barrier**

1.3.5 Targeting membrane tethers

MitoQ is an agent undergoing clinical trials which contains an antioxidant prodrug linked to a hydrophobic triphenylphosphine moiety.

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1.4 Reducing drug toxicity

Rationale:

- **Toxicity is often due to specific functional groups**
- **Remove or replace functional groups known to be toxic e.g.**
  - **aromatic nitro groups**
  - **aromatic amines**
  - **bromoarenes**
  - **hydrazines**
  - **polyhalogenated groups**
  - **hydroxylamines**
- **Vary substituents**
- **Vary position of substituents**

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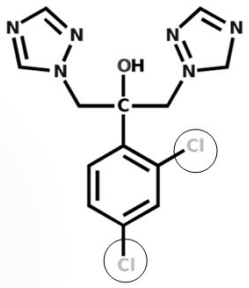
1.4 Reducing drug toxicity

Example - varying substituents

- **Fluconazole (Diflucan) - antifungal agent**



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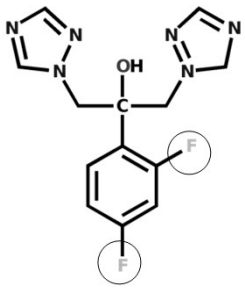

Fluconazole

Substituents varied
Less toxic

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1.5 Prodrugs

Definition:

Inactive compounds which are converted to active compounds in the body.

Uses:

- **Improving membrane permeability**
- **Prolonging activity**
- **Masking toxicity and side effects**
- **Varying water solubility**
- **Drug targeting**
- **Improving chemical stability**
- **'Sleeping agents'**

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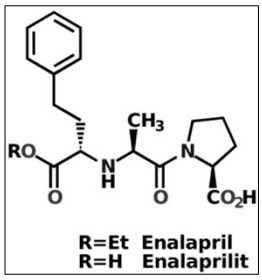
1.5.1 Prodrugs to improve membrane permeability

1.5.1.1 Esters

- **Used to mask polar and ionisable carboxylic acids**
- **Hydrolysed in blood by esterases**
- **Used when a carboxylic acid is required for target binding**
- **Leaving group (alcohol) should ideally be non toxic**

Example:

Enalapril for enalaprilate (antihypertensive)



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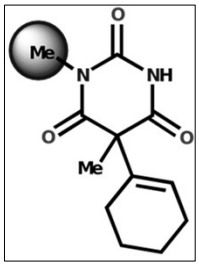
1.5.1.2 *N*-Methylation of amines

- **Used to reduce polarity of amines**
- **Demethylated in liver**

Example:

Hexobarbitone



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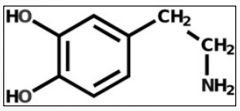
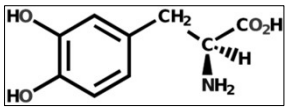
1.5.1.3 Trojan Horse Strategy

- **Prodrug designed to mimic biosynthetic building block**
- **Transported across cell membranes by carrier proteins**

Example: Levodopa for dopamine





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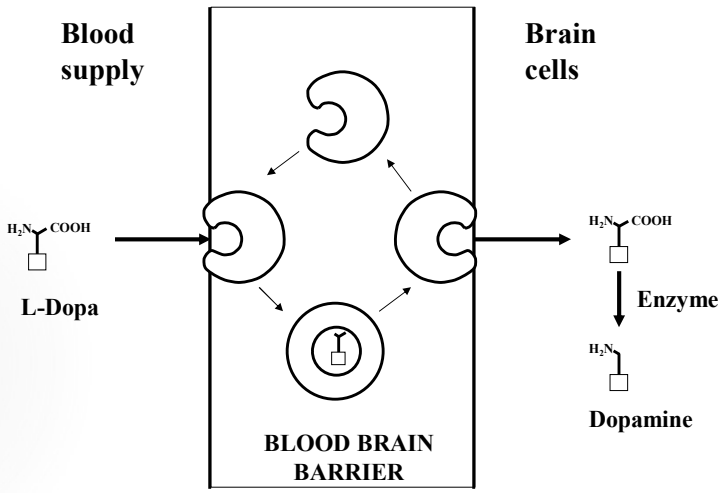
1.5.1 Prodrugs to improve membrane permeability



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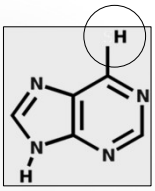
1.5.2 Prodrugs to prolong activity

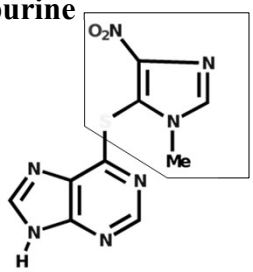
1.5.2.1 Mask polar groups

- **Reduces rate of excretion**

Example:

Azathioprine for 6-mercaptopurine





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1.5.2 Prodrugs to prolong activity

1.5.2.2 Add hydrophobic groups

- **Drug concentrated in fat tissue**
- **Slow removal of hydrophobic group**
- **Slow release into blood supply**

Example:

Cycloguanil pamoate (antimalarial)

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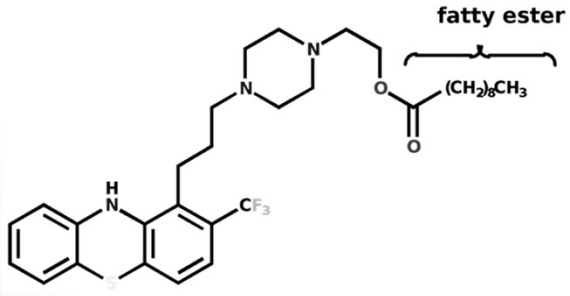
1.5.2 Prodrugs to prolong activity

1.5.2.2 Add hydrophobic groups

Example:

Hydrophobic esters of fluphenazine (antipsychotic)



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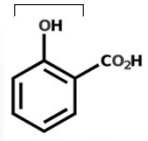
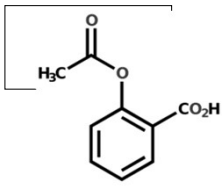
1.5.3 Prodrugs to mask toxicity and side effects

- **Mask groups responsible for toxicity/side effects**
- **Used when groups are important for activity**

Example:

Aspirin for salicylic acid





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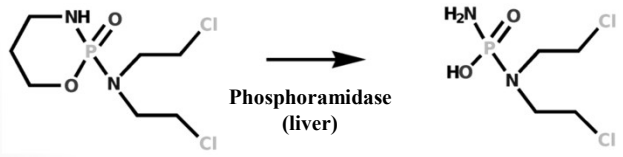
1.5.3 Prodrugs to mask toxicity and side effects

Example:

Cyclophosphoramide for phosphoramide mustard (anticancer agent)



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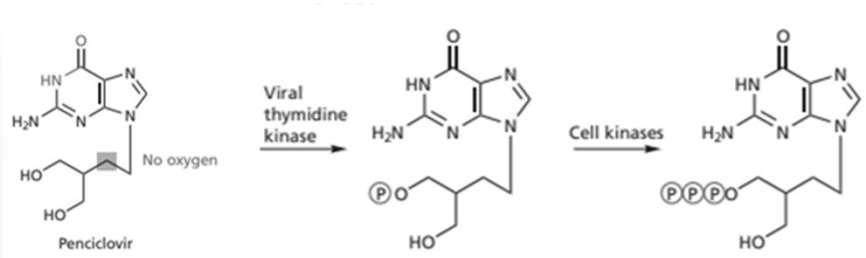
1.5.3 Prodrugs to mask toxicity and side effects

Example

Antiviral drugs



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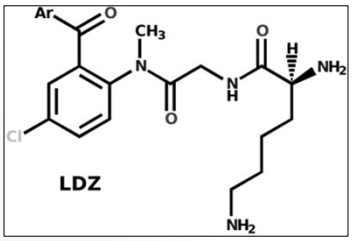
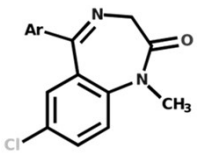
Example:

LDZ for diazepam



a) Aminopeptidase
b) Cyclisation



Diazepam

LDZ

- **Avoids drowsy side effects of diazepam**

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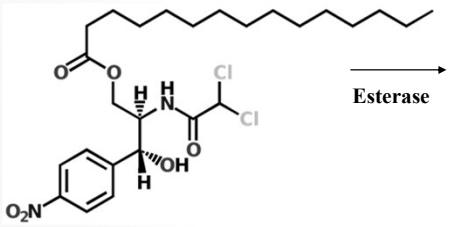
1.5.4 Prodrugs to lower water solubility

- **Used to reduce solubility of foul tasting orally active drugs**
- **Less soluble on tongue**
- **Less revolting taste**

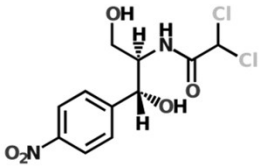
Example:

Palmitate ester of chloramphenicol (antibiotic)

Palmitate ester



Esterase



Chloramphenicol

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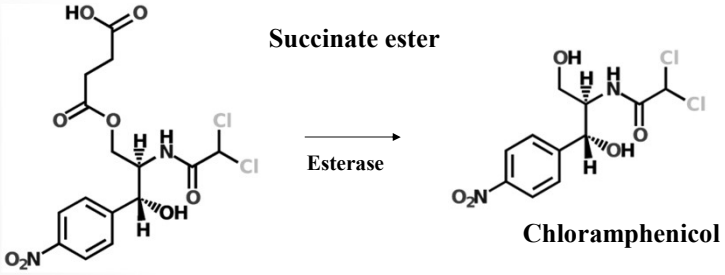
1.5.5 Prodrugs to increase water solubility

- Often used for i.v. drugs
- Allows higher concentration and smaller dose volume
- May decrease pain at site of injection

Example:

Succinate ester of chloramphenicol (antibiotic)



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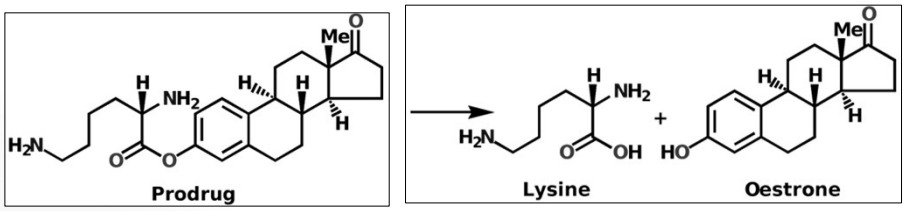
Example:

Lysine ester of oestrone



- Lysine ester of oestrone is better absorbed orally than oestrone
- Increased water solubility prevents formation of fat globules in gut
- Better interaction with the gut wall
- Hydrolysis in blood releases oestrone and a non toxic amino acid

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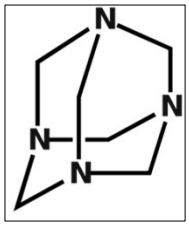
1.5.6 Prodrugs used to target drugs

Example:

Hexamine



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1.5.7 Prodrugs to increase chemical stability

Example

Hetacillin for ampicillin

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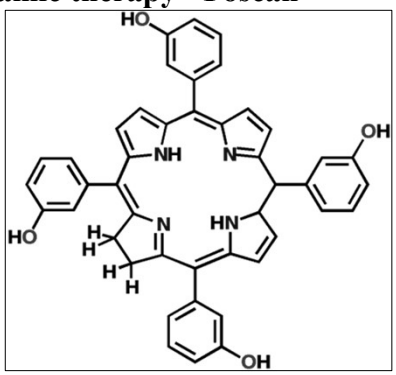
1.5.8 Prodrugs activated by external influences -sleeping agents

Example: Photodynamic therapy - Foscan



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1.6 Drug alliances - synergism

Definition:

Drugs which have a benefical effect on the activity or pharmacokinetic properties of another drug

1.6.1 Sentry Drugs

1.6.2 Localising drugs to a target area

1.6.3 Increasing absorption

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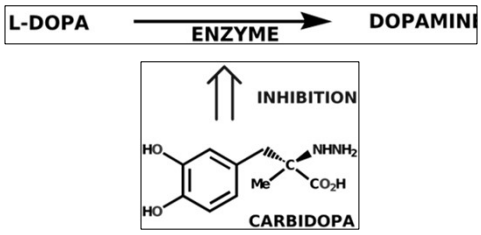
1.6.1 Sentry Drugs

Definition
A drug that is added to 'protect' another drug

Example
Carbidopa



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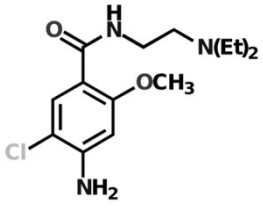
1.6.2 Localising drugs to a target area

Example: Adrenaline and procaine (local anaesthetic)

- **Adrenaline constricts blood vessels at the injection area**
- **Procaine is localised at the injection area**

1.6.3 Increasing absorption

Example: Metoclopramide



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