Topic 7.2
INTRODUCTION TO DRUG DESIGN

Chapter 11 Patrick

Contents

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

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)

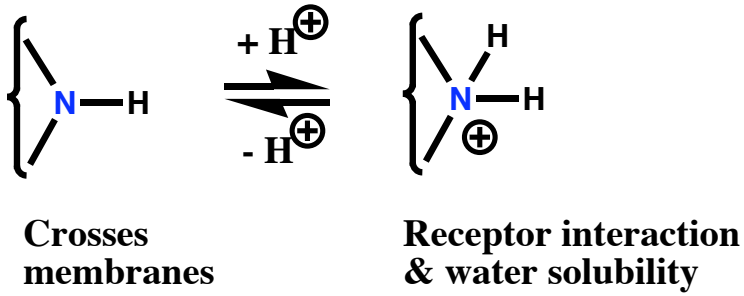
1. Pharmacokinetics – drug design

- 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



Crosses membranes

Receptor interaction & water solubility

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

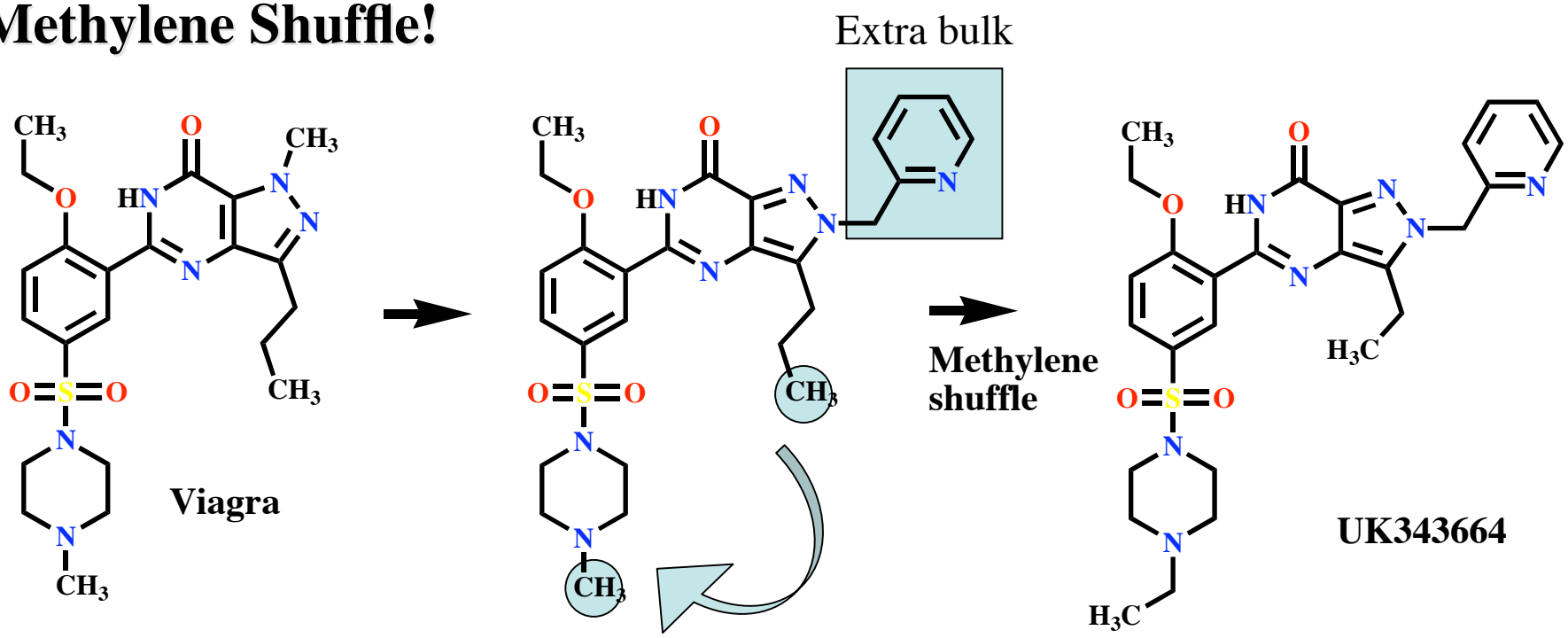
Methods:

- Often feasible to remove alkyl groups from heteroatoms and replace with different alkyl groups
- Usually difficult to remove alkyl groups from the carbon skeleton - full synthesis often required

1.1 Solubility and membrane permeability

1.1.1 Vary alkyl substituents

Methylene Shuffle!



1.1 Solubility and membrane permeability

1.1.2 'Masking' or removing polar groups

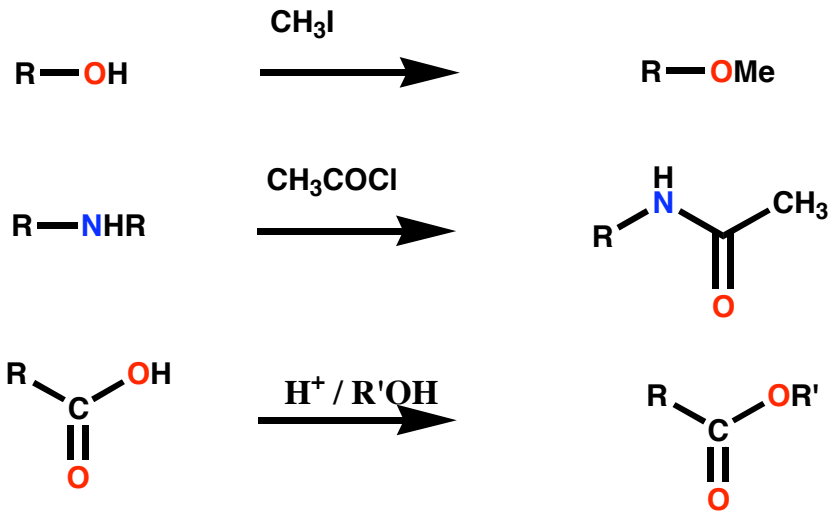
Rationale:

- 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:

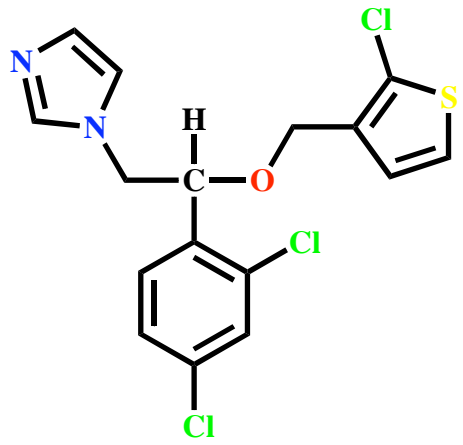


1.1 Solubility and membrane permeability

1.1.3 Adding polar groups

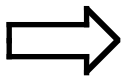
Rationale:

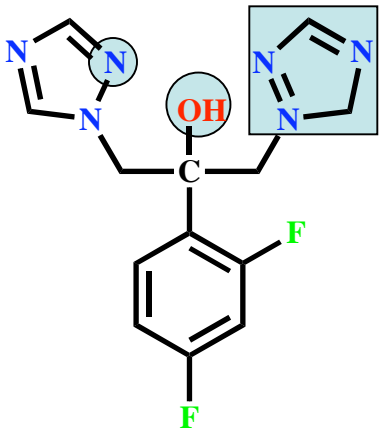
- Adding polar groups increases polarity and decreases hydrophobic character
- Useful for targeting drugs vs. gut infections
- Useful for reducing CNS side effects



Tioconazole

Antifungal agent with poor solubility - skin infections only





Fluconazole

Systemic antifungal agent improved blood solubility

Disadvantage:

- May introduce unwanted side effects

1.1 Solubility and membrane permeability

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 ionised to unionised drug

Method:

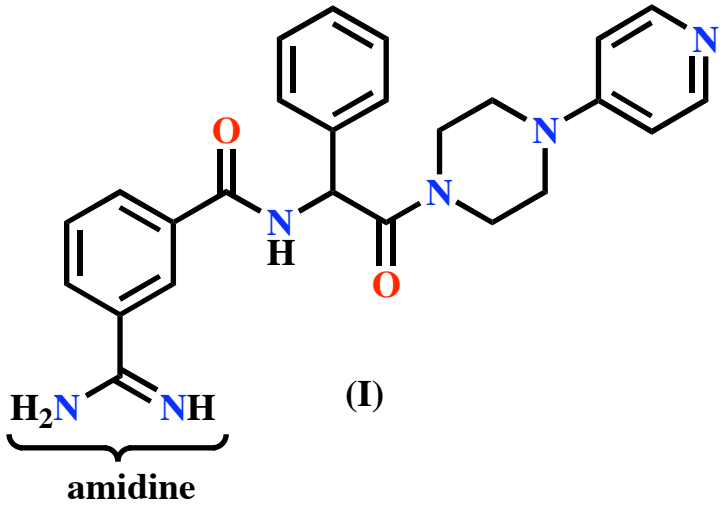
- Vary alkyl substituents on amine nitrogens
- Vary aryl substituents to influence aromatic amines or aromatic carboxylic acids

Disadvantage:

- May affect binding interactions

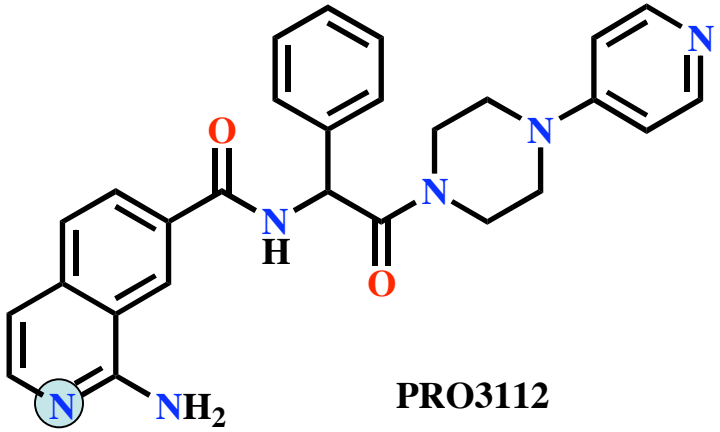
1.1 Solubility and membrane permeability

1.1.4 Vary pK_a



(I)

Antithrombotic
but too basic



PRO3112

Decreased basicity
N locked into heterocycle

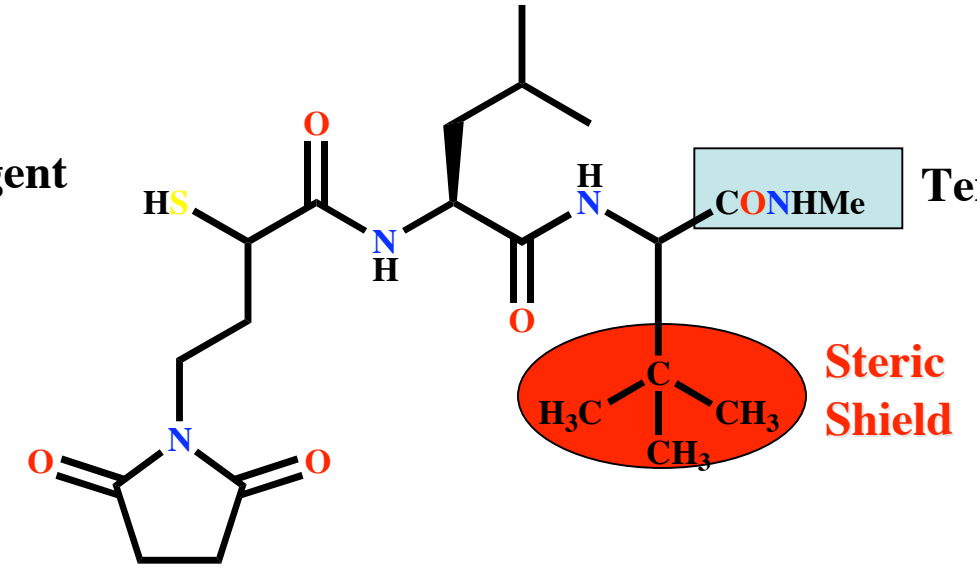
1.2 Drug stability

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



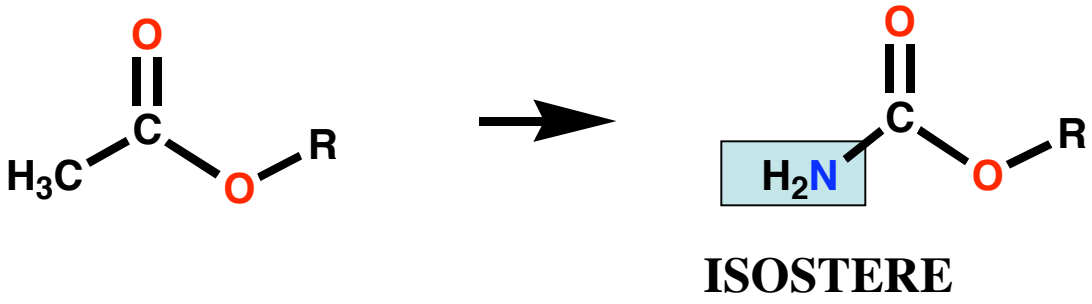
Blocks hydrolysis of terminal amide

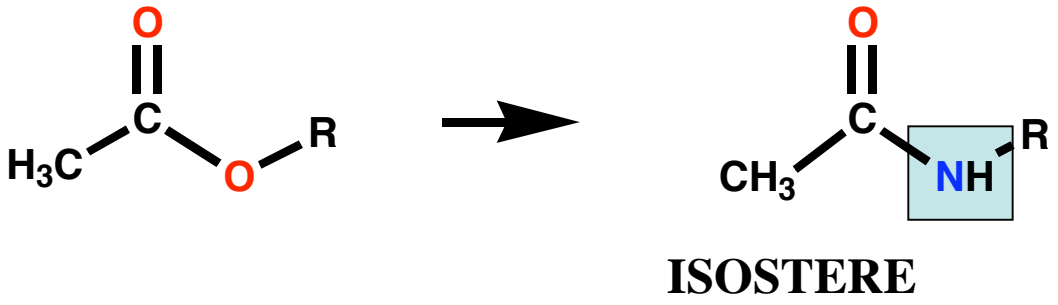
1.2 Drug stability

1.2.2 'Electronic shielding' of NH_2

Rationale:

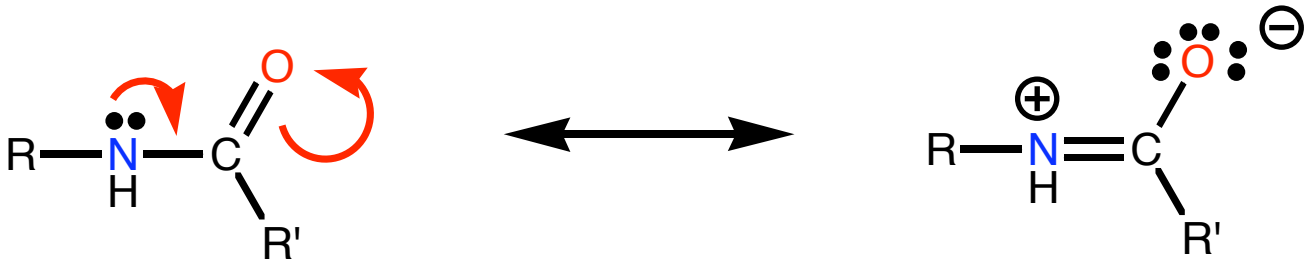
- Used to stabilise labile functional groups (e.g. esters)
- Replace labile ester with more stable urethane or amide
- Nitrogen feeds electrons into carbonyl group and makes it less reactive
- Increases chemical and metabolic stability





1.2 Drug stability

1.2.2 'Electronic shielding' of NH_2



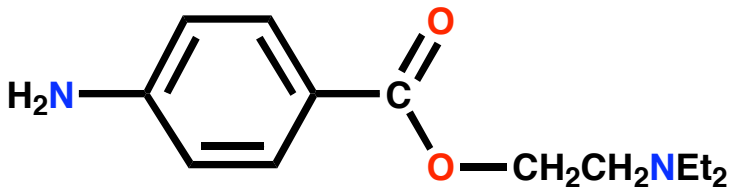
See carbamoylcholine

1.2 Drug stability

1.2.3 Stereoelectronic Effects

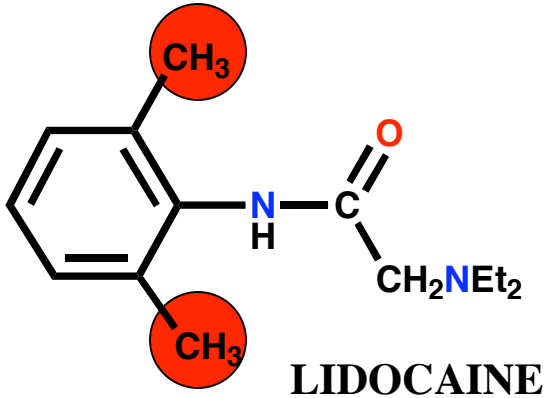
Rationale:

- 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

1.2 Drug stability

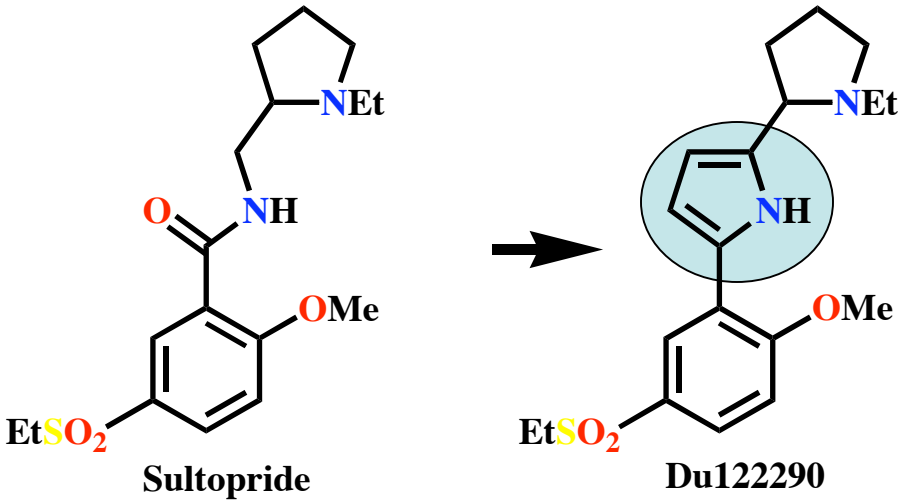
1.2.4 Bio-isosteres

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)



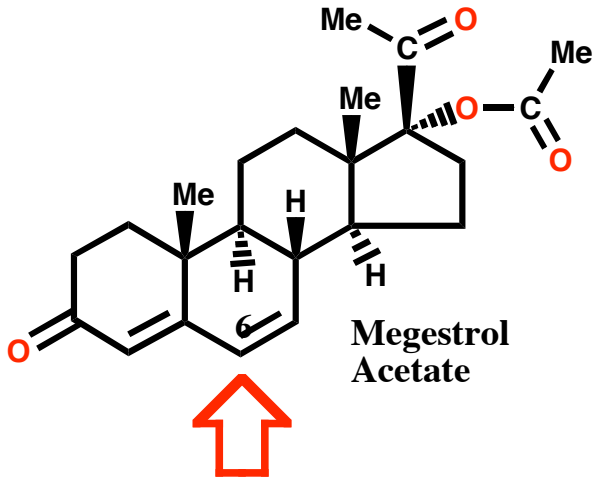
Pyrrole ring = bioisostere for amide

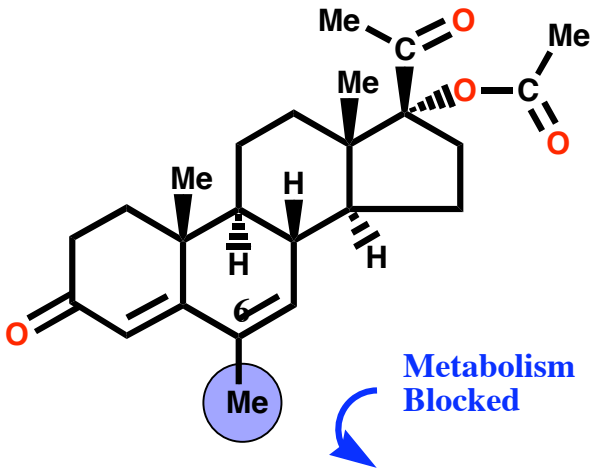
1.2 Drug stability

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





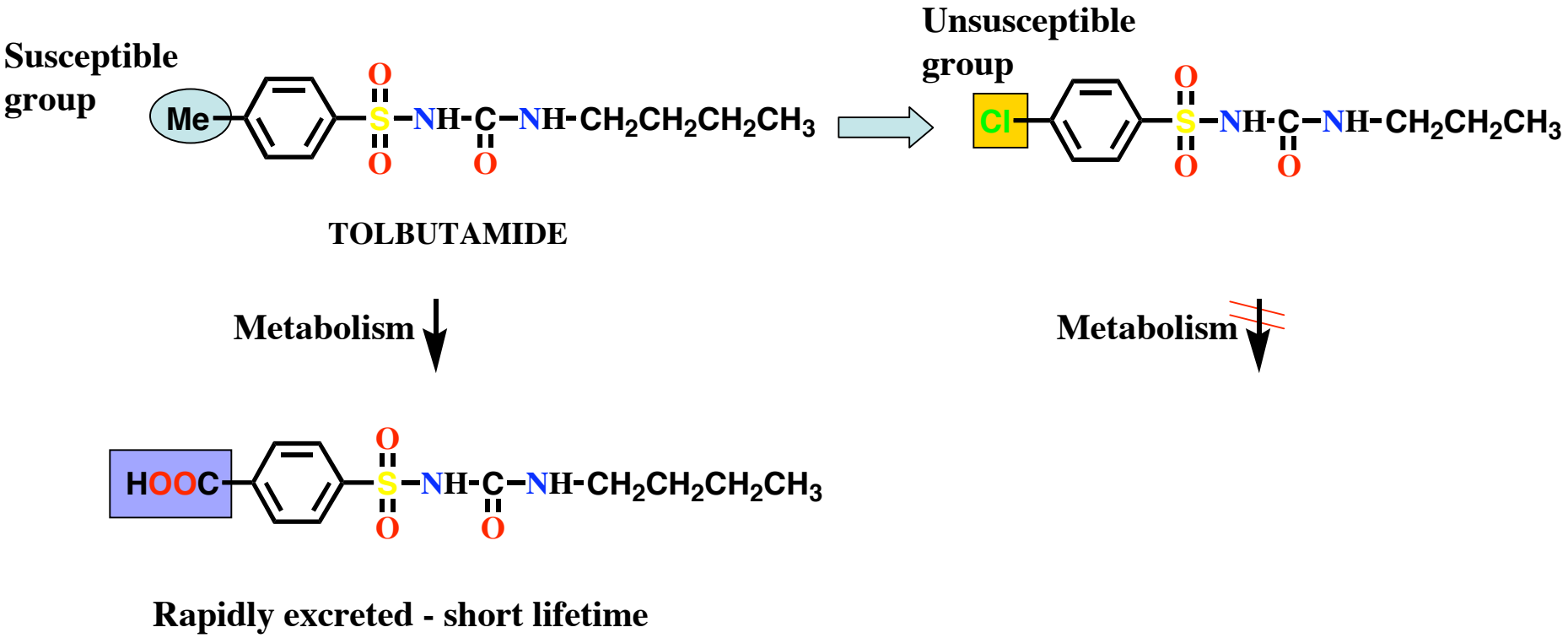
Oral contraceptive
- limited lifetime

1.2 Drug stability

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 (antibiotic)]



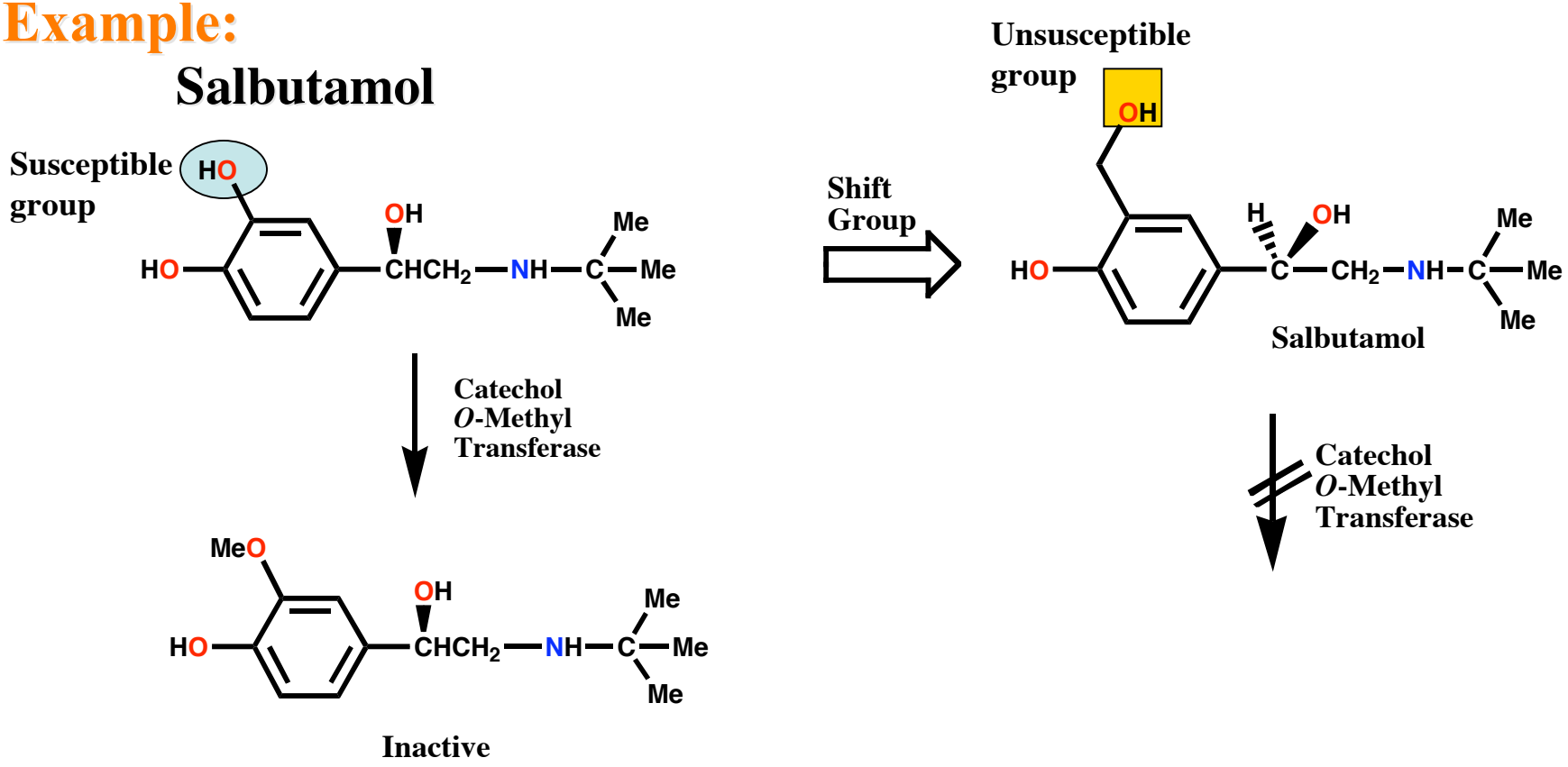
1.2 Drug stability

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 recognizable to target

Example:



1.2 Drug stability

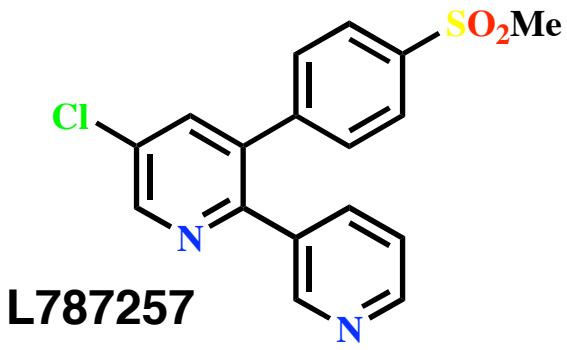
1.2.8 Introducing susceptible metabolic groups

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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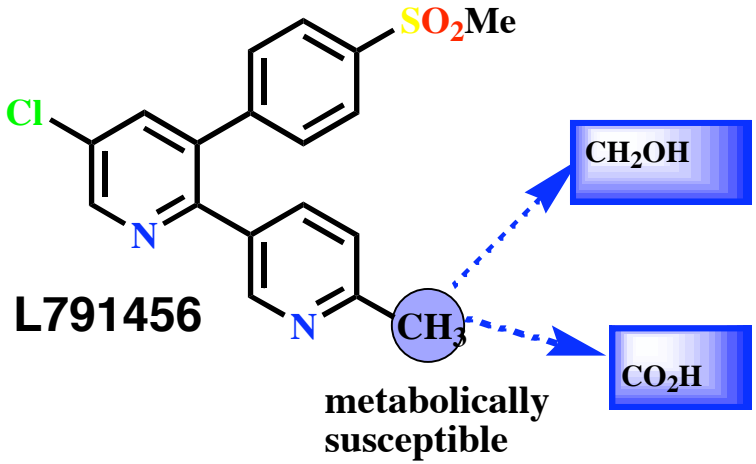

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metabolically susceptible

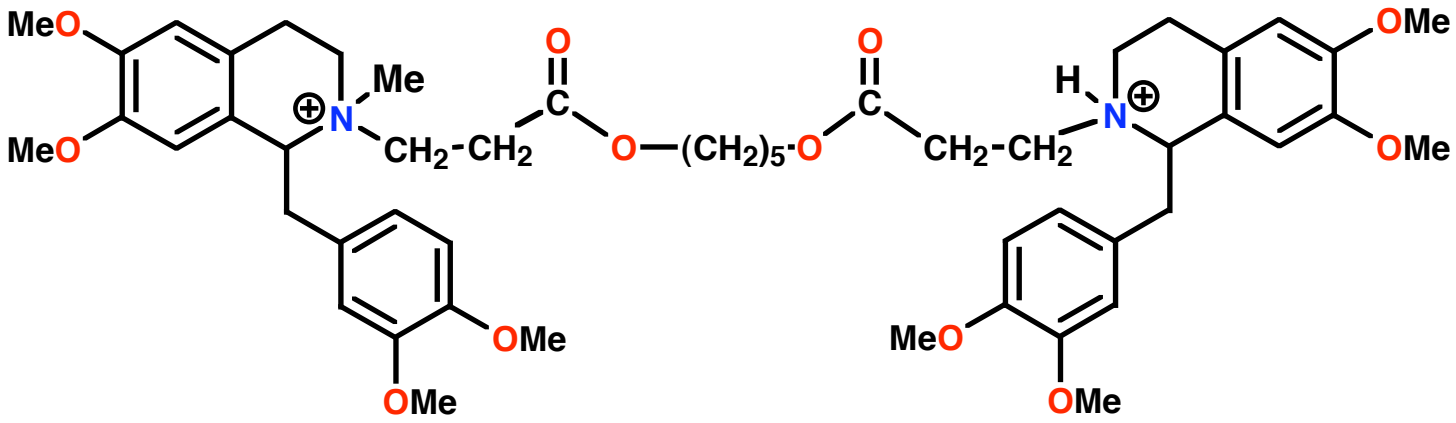
1.2 Drug stability

1.2.9 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

1.3 Drug targeting

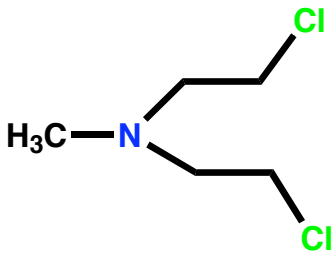
1.3.1 Linking a biosynthetic building block

Rationale:

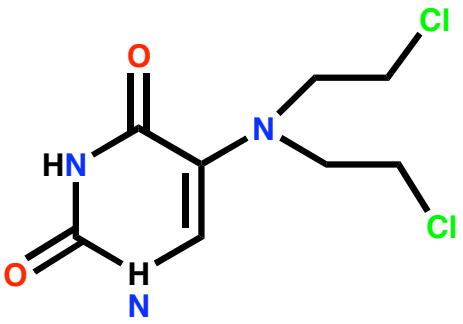
- Drug 'smuggled' into cell by carrier proteins for natural building block (e.g. amino acids or nucleic acid bases)
- Increases selectivity of drugs to target cells and reduces toxicity to other cells

Example:

Anticancer drugs



Non selective alkylating agent
Toxic



Uracil Mustard

- Alkylating group is attached to a nucleic acid base
- Cancer cells grow faster than normal cells and have a greater demand for nucleic acid bases
- Drug is concentrated in cancer cells - Trojan horse tactic

1.3 Drug targeting

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

1.3 Drug targeting

1.3.3 Targeting gut infections

Rationale:

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

1.3 Drug targeting

1.3.4 Targeting peripheral regions over CNS

Rationale:

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

1.4 Reducing drug toxicity

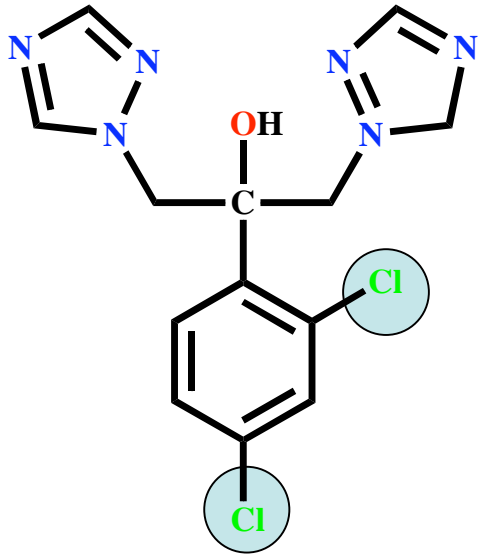
Rationale:

- 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

1.4 Reducing drug toxicity

Example - varying substituents

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



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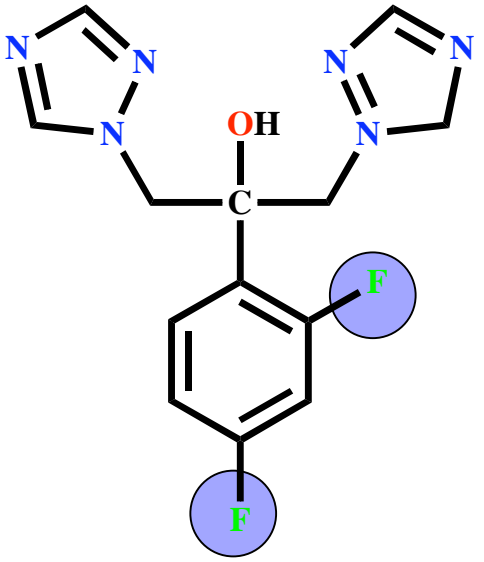


Fluconazole

Substituents varied
Less toxic

Contents

Part 2: Sections 11.5 – 11.6

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

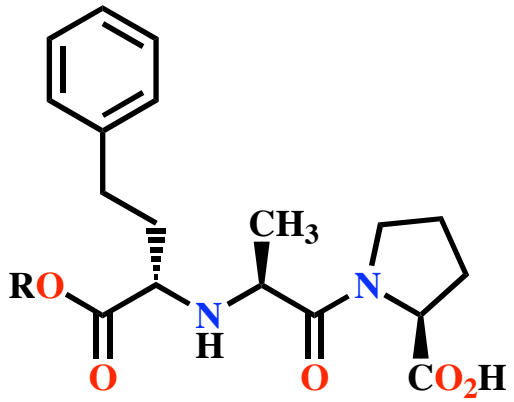
1.5.1 Prodrugs to improve membrane permeability

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)

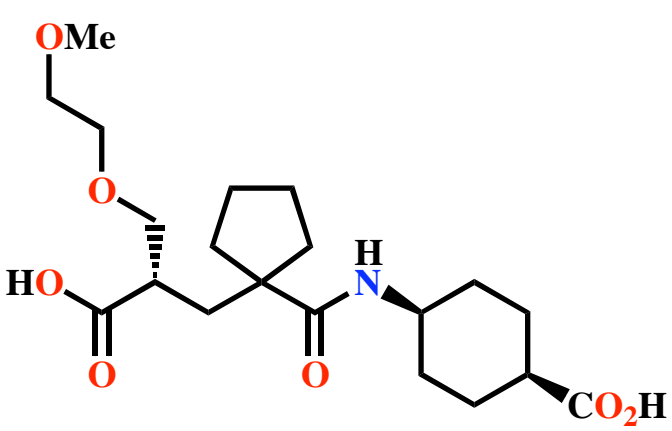


R=Et Enalapril
R=H Enalaprilit

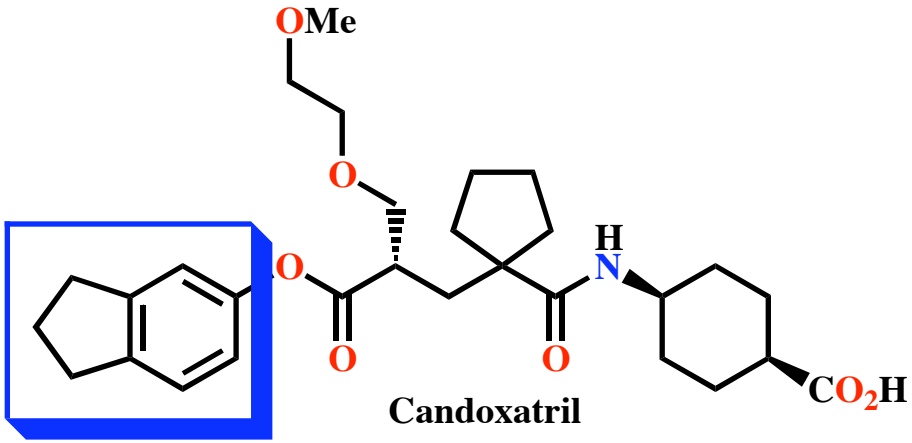
1.5.1 Prodrugs to improve membrane permeability

Example:

Candoxatril for Candoxatrilat (protease inhibitor)



Candoxatrilat



Candoxatril

5-indanyl group

- Varying the ester varies the rate of hydrolysis
- Electron withdrawing groups increase rate of hydrolysis (e.g. 5-indanyl)
- Leaving group (5-indanol) is non toxic

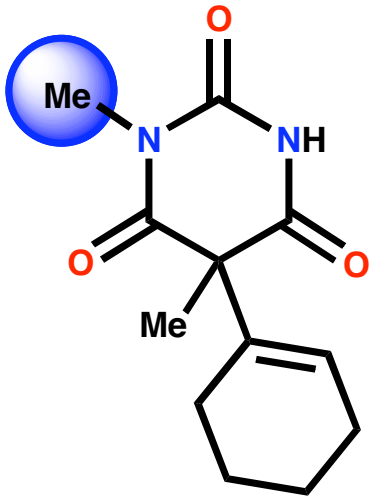
1.5.1 Prodrugs to improve membrane permeability

1.5.1.2 *N*-Methylation of amines

- Used to reduce polarity of amines
- Demethylated in liver

Example:

Hexobarbitone

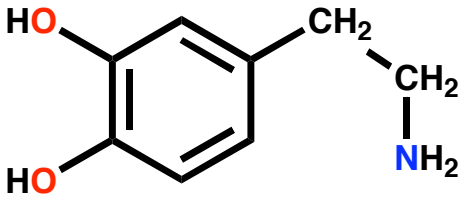


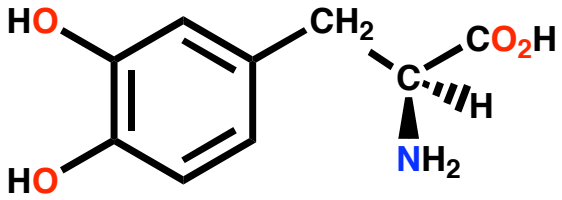
1.5.1 Prodrugs to improve membrane permeability

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





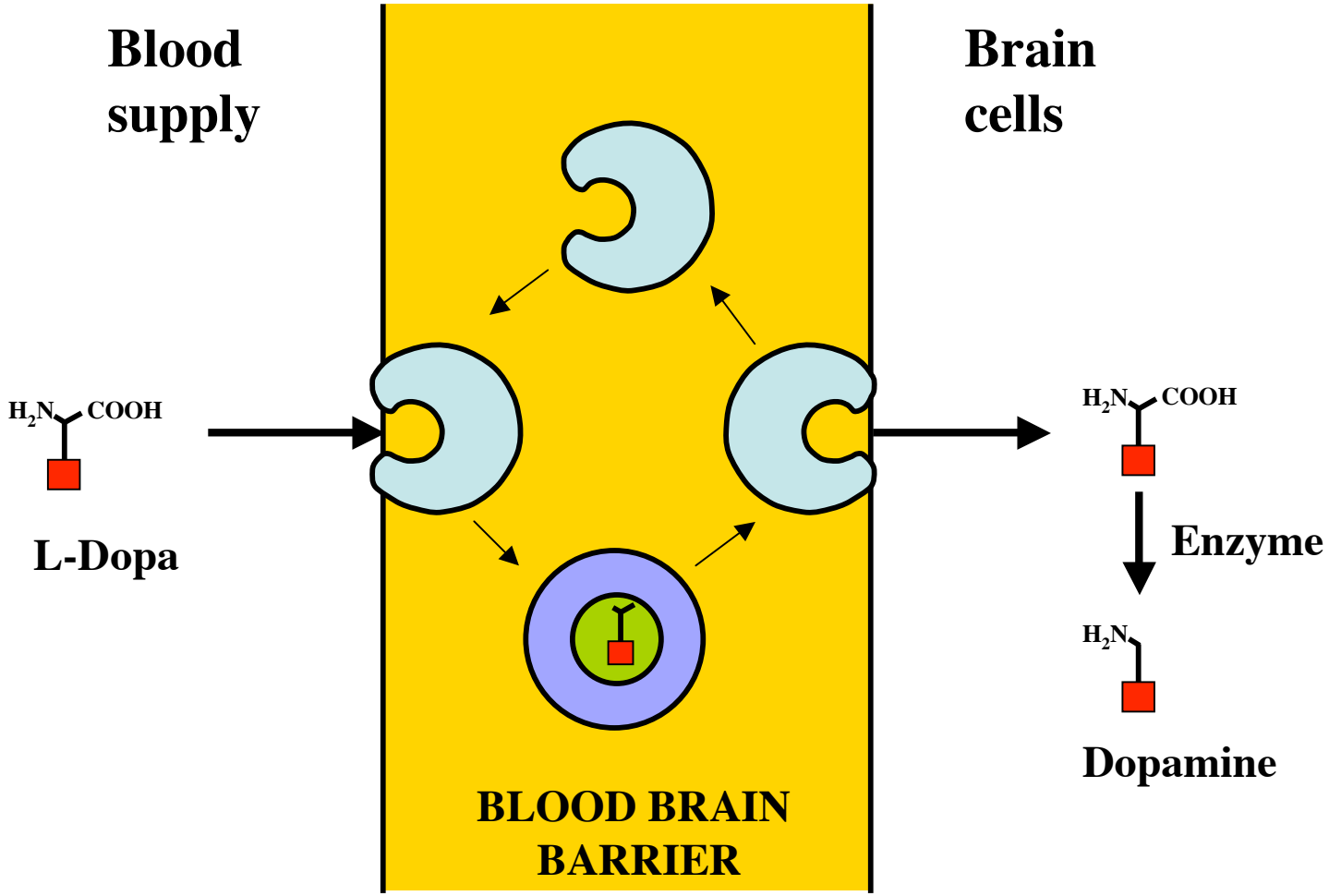
Dopamine

- **Useful in treating Parkinson's Disease**
- **Too polar to cross cell membranes and BBB**

Levodopa

- **More polar but is an amino acid**
- **Carried across cell membranes by carrier proteins for amino acids**
- **Decarboxylated in cell to dopamine**

1.5.1 Prodrugs to improve membrane permeability



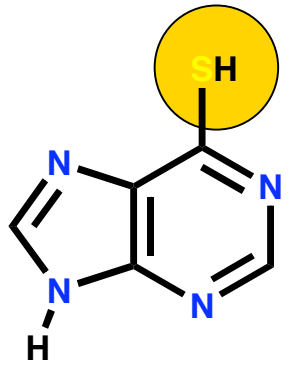
1.5.2 Prodrugs to prolong activity

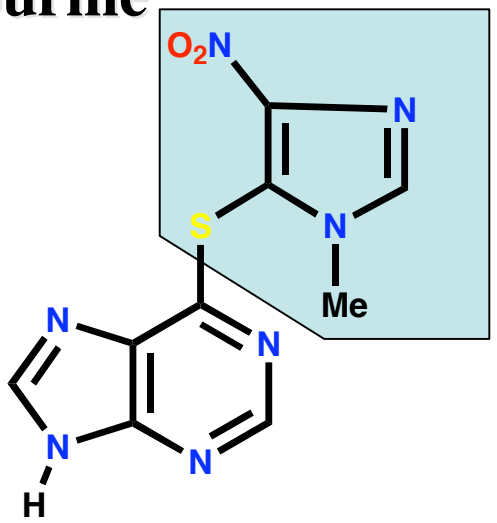
1.5.2.1 Mask polar groups

- Reduces rate of excretion

Example:

Azathioprine for 6-mercaptopurine





6-Mercaptopurine

(suppresses immune response)

- **Short lifetime - eliminated too quickly**

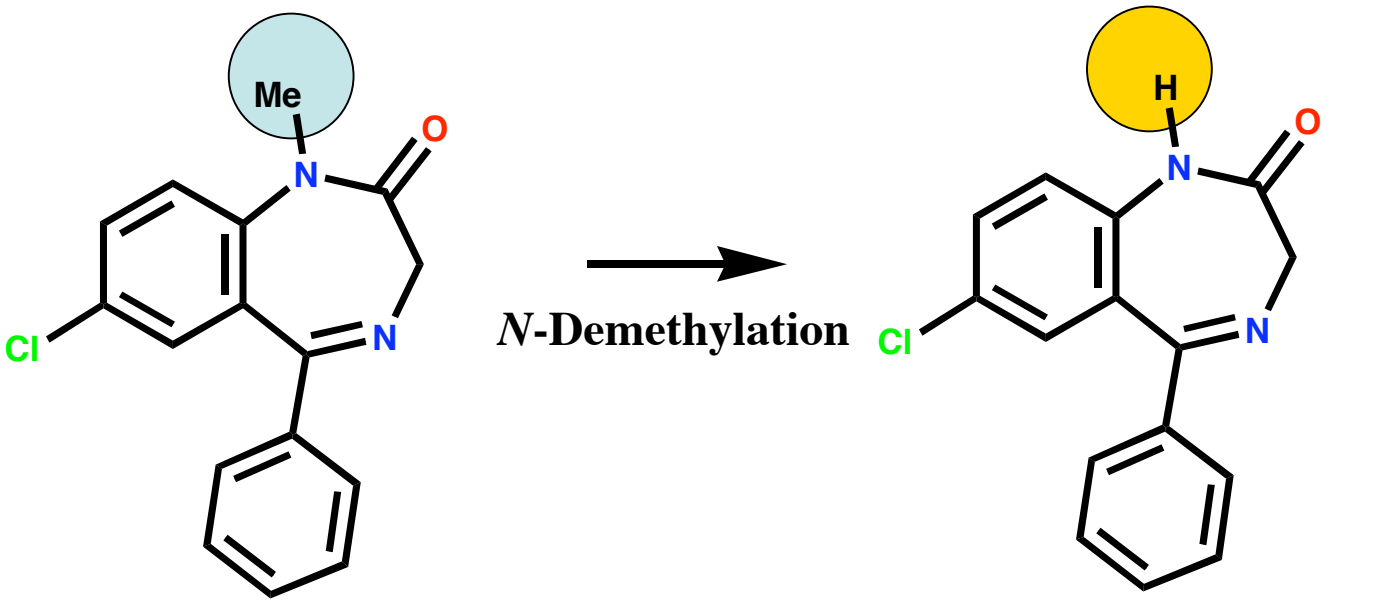
Azathioprine

- **Slow conversion to 6-mercaptopurine**
- **Longer lifetime**

1.5.2 Prodrugs to prolong activity

Example:

Valium for nordazepam



Valium **Nordazepam**

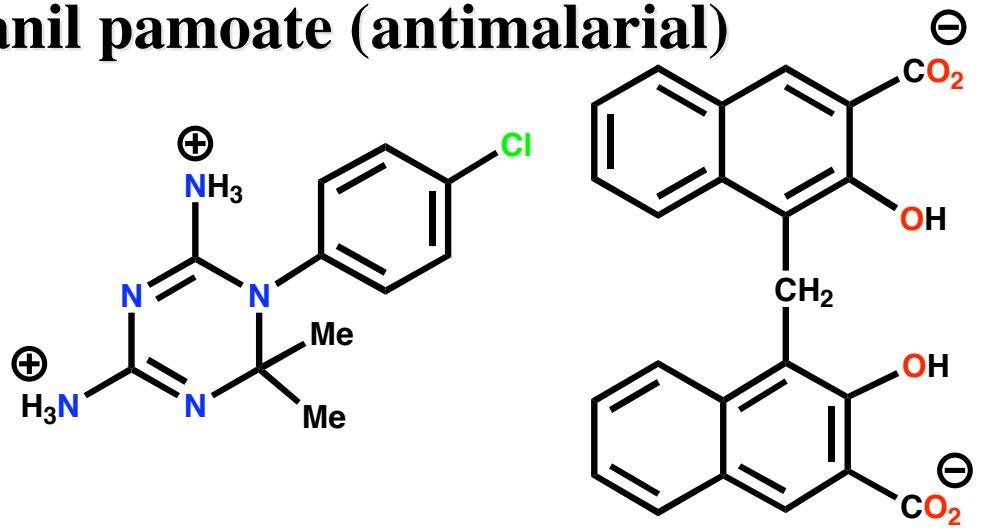
1.5.2 Prodrugs to prolong activity

1.5.2.2 Add hydrophobic groups

- Drug (and counterion) concentrated in fat tissue
- Slow removal of hydrophobic group
- Slow release into blood supply

Example:

Cycloguanil pamoate (antimalarial)



Cycloguanil **Pamoate**

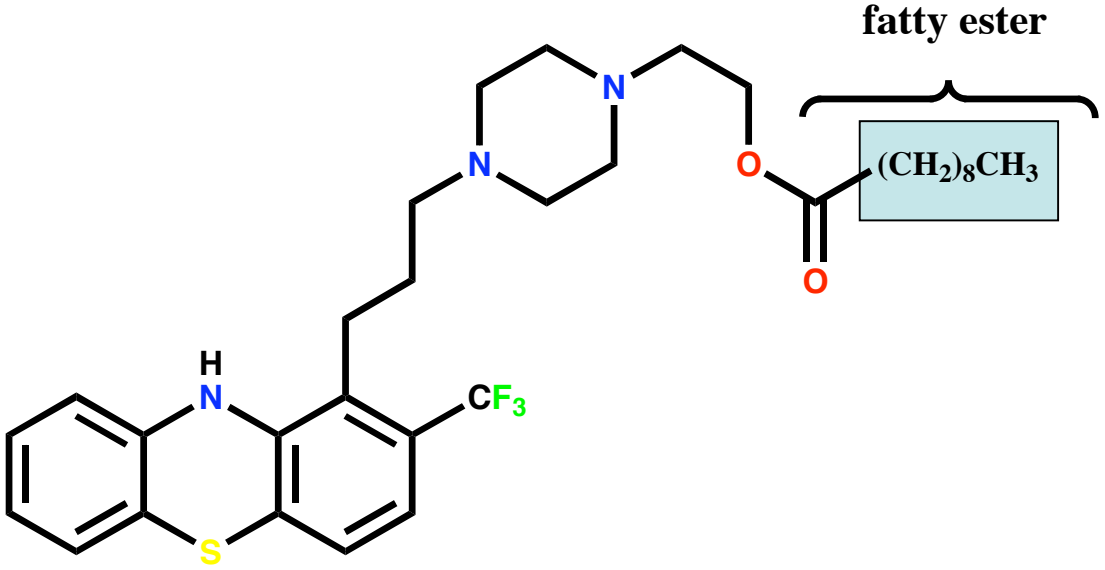
Lipophilic

1.5.2 Prodrugs to prolong activity

1.5.2.2 Add hydrophobic groups

Example:

Hydrophobic esters of fluphenazine (antipsychotic)



- Given by intramuscular injection
- Concentrated in fatty tissue
- Slowly released into the blood supply
- Rapidly hydrolysed in the blood supply