Topic 7.2
INTRODUCTION TO DRUG DESIGN

Chapter 11 Patrick
Contents
Part 1: Sections 11.1 – 11.4
1. Pharmacokinetics – drug design
   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 pKa
   1.2. Drug stability
      1.2.1. Steric Shields
      1.2.2. ‘Electronic shielding’ of NH2
      1.2.3. Steroelectronic 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
      1.2.9. Introducing chemically susceptible groups
   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
   1.4. Reducing drug toxicity
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

![Chemical Structures]

- 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!**

![Methylene Shuffle Diagram](image-url)
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

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$_a$

Antithrombotic but too basic

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

Blocks hydrolysis of terminal amide
1.2 Drug stability

1.2.2 ‘Electronic shielding’ of \( \text{NH}_2 \)

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 Steroelectronic 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)
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:

**Salbutamol**

- Susceptible group
- Shift Group
- Unsusceptible group
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**

L787257

L791456
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
  
  ![Chemical structure](Uracil%20Mustard)
  Non selective alkylating agent
  Toxic

  ![Chemical structure](H3C-N-CI)

- 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

Substituents varied
Less toxic
Contents
Part 2: Sections 11.5 – 11.6

1.5. Prodrugs
   1.5.1. Prodrugs to improve membrane permeability
      1.5.1.1. Esters
      1.5.1.2. N-Methylation of amines
      1.5.1.3. Trojan Horse Strategy
   1.5.2. Prodrugs to prolong activity
      1.5.2.1. Mask polar groups
      1.5.2.2. Add hydrophobic groups
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)
1.5.1 Prodrugs to improve membrane permeability

Example:

Candoxatril for Candoxatrilat (protease inhibitor)

- 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

Blood supply

Brain cells

L-Dopa

Dopamine

Enzyme

COOH

H₂N

COOH

H₂N

BLOOD BRAIN BARRIER
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

\[ \text{N-Demethylation} \]
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)

\[
\text{Cycloguanil} \quad \text{Pamoate}
\]

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