Medicinal Chemistry/ CHEM 458/658
Chapter 1- Introduction

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What are drugs?

Drugs

• Chemical substances to prevent or cure diseases.

- activity
- potency
- side effects

- drug resistance
- new metabolism
- downregulation (e.g. gonadotrophin)
- development of resistant strains
  (antibiotics, anti-malaria, -TB drugs)

• Need for new drugs
Drug Development – Historical Outline

- As old as human history (even older)
- Use of certain isolated substances from vegetable/animal/mineral sources (*pharmakon*)
- Herbals and Pharmacopeias in the 1500s
- New World – new drugs

- Systematic drug development (Hanaoka Seishu, 1760-1835)
Drug Development – Historical Outline

- Louis Pasteur – wine - microorganism theory – bacteriology (1864)
  Joseph Lister – carbolic acid (phenol)

- First synthetic drug development
  Paul Ehrlich (1909, salvarsan, the “606th experiment”)
  Chemotherapy – Magic bullet

- Foundation of the modern drug discovery

  Chemotherapeutic index: $\min_{\text{curative dose}} / \max_{\text{tolerated dose}}$

  Therapeutic index: $\text{LD}_{50} / \text{ED}_{50}$

SAR and QSAR
Drug Development – Historical Outline

- Receptor theory (Langley, 1905) recepive substances ligands (stereoelectronic structure, active conformation pharmacophore)

![Diagram showing molecular structures](image)

**Figure 1.2** (a) The similar shapes and outline electronic structures (stereoelectronic structures) of amide Arg22 and ester groups. (b) Procaine and procainamide

- Local anaesthetic
- Antiarrhythmic

FBPase active site with inhibitor
Drug Development – Historical Outline

• Serendipity – penicillin (Fleming 1924, Florey, Chain 1940)

• Half serendipity-half systematic
  Dyes to Sulfa Drugs (IG Farben, Dogmak 1930s)

\[
\text{Prontosil Red} \quad \xrightarrow{\text{metabolism}} \quad \text{Sulfanilamide}
\]

• Modern drug development
  Molecular modelling
  Structural biology/biochemistry
  Combinatorial chemistry/molecular libraries
More teamwork based (different expertise), more structured (e.g. The Pill) (but good luck is still welcome – Viagra)

**Drug Development – General Stages**

- Basic research into the disease process and its causes
- Assessment of the biochemical and biological processes of the disease and/or its cause
- Team decides where intervention is most likely to bring about the desired result
- Team decides the structure of a suitable lead compound
- Design of the synthetic pathway to produce the lead compound
- Initial biological and toxicological testing
- Synthesis of analogues
- Selection of the analogue with the optimum activity
- Clinical trials and MAA

*Figure 1.3* The general steps in the discovery of a new drug for a specific disease state
Drug Development – Leads and Analogues

• Bioavailability

A fraction of a dose that is found in general circulation

Lipinski rules:
- a molecular mass less than 500
- a calculated value of log P less than 5
- less than 10 hydrogen bond acceptors (e.g. O-, N- etc)
- less than 5 hydrogen bond donors (e.g. NH, OH etc.)

P – partition coefficient in water/octanol system

If a compound fails two or more rules – bioavailability is unlikely (activity is unlikely)
Drug Development – Leads and Analogues

• Solubility

  Lipophilic vs. hydrophilic character

• Structure

  Determines how the lead compound can bind to a receptor/target.

• Stability

  Shelf life (usually 10% acceptable)

  After administration – long enough to reach target
  increasing stability – modifying structure
  more stable prodrug
  suitable dosage form
### Stability/activity of chiral drugs

<table>
<thead>
<tr>
<th>First stereoisomer</th>
<th>Second stereoisomer</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>Activity of same type and potency</td>
<td>The R and S isomers of the antimalarial chloroquine have equal potencies</td>
</tr>
<tr>
<td></td>
<td><img src="image1" alt="Chloroquine structure" /></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>Activity of same type</td>
<td>The E isomer of diethylstilbestrol, an estrogen but weaker, is only 7% as active as the Z isomer</td>
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<tr>
<td></td>
<td><img src="image2" alt="Diethylstilbestrol structure" /></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>Activity of a different type</td>
<td>S-Ketamine is an anaesthetic whereas R-Ketamine has little anaesthetic action but is a psychotropic agent</td>
</tr>
<tr>
<td></td>
<td><img src="image3" alt="Ketamine structure" /></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>No activity</td>
<td>S-α-Methylisoprop is a hypertensive drug but the R isomer is inactive</td>
</tr>
<tr>
<td></td>
<td><img src="image4" alt="S-α-Methylisoprop structure" /></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>Active but different side effects</td>
<td>Thalidomide: the S isomer is a sedative and has teratogenic side effects; the R isomer is also a sedative but has no teratogenic activity</td>
</tr>
<tr>
<td></td>
<td><img src="image5" alt="Thalidomide structure" /></td>
<td></td>
</tr>
</tbody>
</table>
Enhance *in situ* stability – inclusion complexes

*Figure 1.4* Schematic representations of the types of inclusion complexes formed by cyclodextrins and prostaglandins. The type of complex formed is dependent on the cavity size.
Drug Development – Sources of Leads and Drugs

• Ethnopharmaceutical sources

Cinchona bark, foxglove, poppy fruit etc.

Figure 1.5 *Digitalis purpurea*, the common foxglove. The leaves contain about 30 different cardioactive compounds. The major components of this mixture are glycosides, with aglycones of digitoxigenin, gitoxigenin and gitaloxigenin. Two series of compounds are known, those where R₁, the carbohydrate residue (glycone) of the glycoside, is either a tetrasaccharide or a trisaccharide chain. Many of the compounds isolated were formed by drying of the leaves prior to extraction. Digitoxin, a trisaccharide derivative of digitoxigenin, is the only compound to be used clinically to treat congestive heart failure and cardiac arrhythmias.
Drug Development – Sources of Leads and Drugs

- Plant sources

  Serendipity, or systematic search

  **taxol – Pacific Yew tree**

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**Figure 1.6** Examples of some of the drugs in clinical use obtained from plants. Taxol and vincristine are anticancer agents isolated from *Taxus brevifolia* and *Vinca rosea* Linn, respectively. Pilocarpine is used to treat glaucoma and is obtained from *Pilocarpus jaborandi* Holmes *Rutaceae*. Morphine, which is used as an analgesic, is isolated from the opium poppy.
Drug Development – Sources of Leads and Drugs

• Plant sources

Serendipity,
or systematic search

A naphthoxirene derivative
Key: $R = \beta$-d-glucopyranosyl

Uncinatone

A chromene

Figure 1.7 Examples of the antifungal compounds discovered by Hostettmann and Marston
Drug Development – Sources of Leads and Drugs

• Marine sources

Serendipity, or systematic search

![Cephalosporin C](image)
![Saxitoxin](image)
![Avarol](image)
![Tetrodotoxin](image)
![Domoic acid](image)

**Figure 1.8** Examples of active compounds isolated from marine sources (Me represents a methyl group). Avarol is reported to be an immunodeficiency virus inhibitor. It is extracted from the sponge *Disidea avara*. The antibiotic cephalosporin C was isolated from the fungus *Acremonium chrysogenum* (*Cephalosporin acremonium*). It was the lead for a wide range of active compounds, a number of which are used as drugs (see section 7.5.2). Domoic acid, which has anthelmintic properties, is obtained from *Chondria armata*. Tetrodotoxin and saxitoxin exhibit local anaesthetic activity but are highly toxic to humans. Tetrodotoxin is found in fish of the order *Tetradontiformes* and saxitoxin is isolated from some marine dinoflagellates. Ara-A is an FDA-approved antiviral isolated from the sponge *Tethya crypta*. Ziconotide is the active ingredient of Prialt, which is used to treat chronic pain. It is an analogue of the ω-conopeptide MVIIA, which occurs in the marine snail *Conus magnus*. 
Drug Development – Sources of Leads and Drugs

- Microorganisms

Serendipity, or systematic search

Figure 1.9 Examples of drugs produced by microbial fermentation. Gramicidin A, benzylpenicillin (penicillin G) and streptomycin are antibiotics isolated from Bacillus brevis, Penicilllin notatum and Streptomyces griseus, respectively. The anticancer agents dactinomycin and pentostatin are obtained from Streptomyces parvulus and Streptomyces antibioticus, respectively.
Drug Development – Sources of Leads and Drugs

• Animal sources - many hormones

  Adrenaline – adrenal medullary extract

  ![Chemical structure of Adrenaline]

  Inuline – pancreatic extract
Drug Development – Sources of Leads and Drugs

• Compound collections, databases, and synthesis

• Pathology of the diseased state

• Market sources and *me-too drugs*
Drug Development – Administration

- Methods and Routes of Administration
  Dosage forms - liquid, semisolid, solid

Figure 1.10  The main routes of drug administration and distribution in the body. The distribution of a drug is also modified by metabolism, which can occur at any point in the system.
• Methods and Routes of Administration

Therapeutic window

**Figure 1.11** A simulation of a therapeutic window for a drug, given in fixed doses at fixed time intervals (↑)

Drug regimen: A dose and how it is administered

Pharmacokinetic properties: rate of absorption, distribution, metabolism, elimination from the body
• Pharmacokinetic Phase
  ADME – Absorption, Distribution, Metabolism, Excretion

• Absorption
  the passage of the drug from its site of administration into
  the circulatory system

Most drugs – oral administration – gastrointestinal (GI) tract
Membranes and tissue barriers
- electronic form of drug (neutral, ionic etc.)
- pH of the medium
- the drug’s partition coefficient
- dosage
- drug’s particle size
- rate of dissolution

The active form is not necessarily
the form that is absorbed!
• Distribution
the transport of the drug from its site of administration to its site of action

Main route – blood (its chemical and physical properties) usually bound to serum proteins (e.g. albumin, reversible)
Solubility is important – insoluble compounds deposited

Application of prodrugs (Prontosil, some cancer drugs)

Figure 1.12 The species involved in the transfer of acidic and basic drugs from the plasma to the surrounding tissues
Drug Development – Drug Action

- Distribution
  blood-brain-barrier (BBB)

**Figure 1.13** The structures of some of the drugs that are able to cross the blood-brain barrier
• **Metabolism**
  the biotransformation of drugs into other compounds (metabolites) - mainly in the liver

oral administration – liver – circulation – *first pass effect*

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**Figure 1.15** An outline of the metabolic pathway for the formation of the active form of sulindac

Inactive administered form of the drug

Active sulphide metabolite of the drug

Sulindac

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• Metabolism

Figure 1.14 An outline of the known metabolic pathways of the local anaesthetic lignocaine
• Excretion
  the process by which unwanted substances are removed from the body

  Main route – kidney (plus other bodily fluids like feaces)
other forms: exhalation, sweating, breast feeding etc.

  kidney : glomerular filtration (small molecules)
  and tubular secretion (active transfer process, large molecules excreted too)
tubular reabsorption – some will reabsorb (water, amino acids etc.)
bile – biliary clearance
  reabsorption occurs via the *enterohepatic cycle*
• Lead optimization and ADME

Having satisfactory ADME properties is not enough, it should be:

- Potentially active in treating patients
- free of existing patents
- produced in sufficient quantities
- capable of being dispensed in a suitable dosage
- must not be too toxic
- must not exhibit teratogenecity of mutagenecity
- cost effective
Drug Development – Classification of Drugs

- Chemical structure

- Pharmacological action
diuretics, hypnotics, vasodilators, respiratory stimulants etc.

- Physiological classification
  - CNS drugs
  - pharmacodynamic agents
  - chemotherapeutic agents
  - other agents (hormones etc.)

Figure 1.16 Examples of the diversity of action of compounds belonging to the same class (Ac=acetyl)
Drug Development – Prodrugs

- Inert compounds that are converted by enzymes active drugs

Figure 1.17  A schematic representation of the formation of dopamine from levodopa