Medicinal Chemistry/ CHEM 458/658

Chapter 1- Introduction

Bela Torok

Department of Chemistry

University of Massachusetts Boston

Boston, MA

What are drugs?

Drugs

- Chemical substances to prevent or cure diseases.

  activity
  potency
  side effects

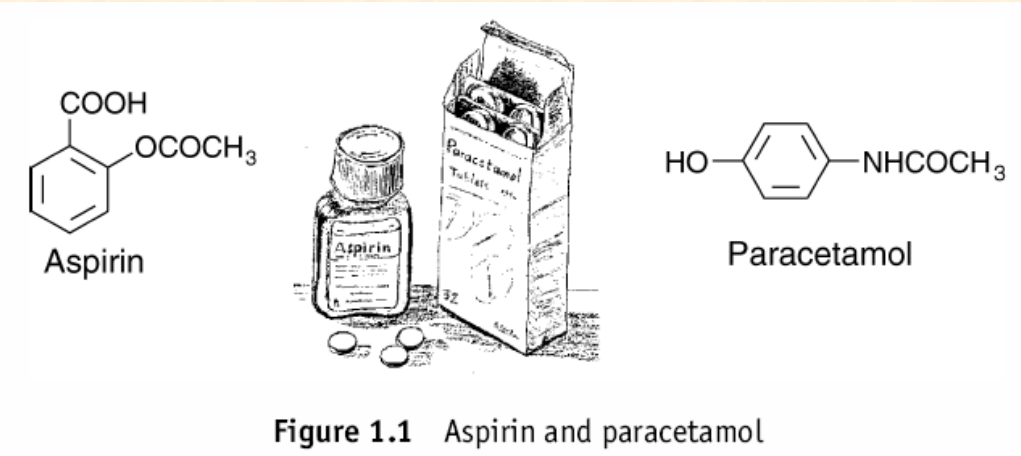


Figure 1.1 Aspirin and paracetamol

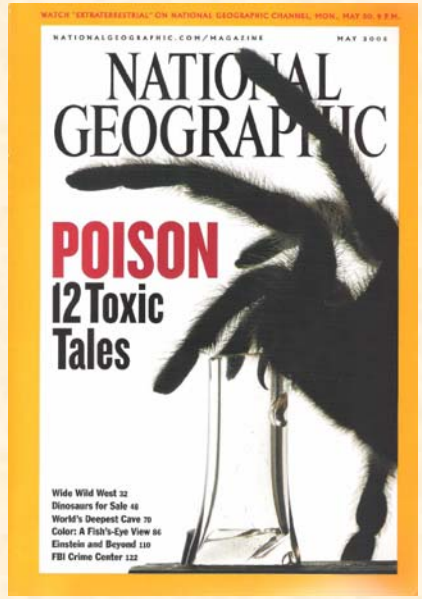
  drug resistance — new metabolism
  downregulation (e.g. gonadotrophin)
  development of resistant strains
  (antibiotics, anti-malaria, -TB drugs)

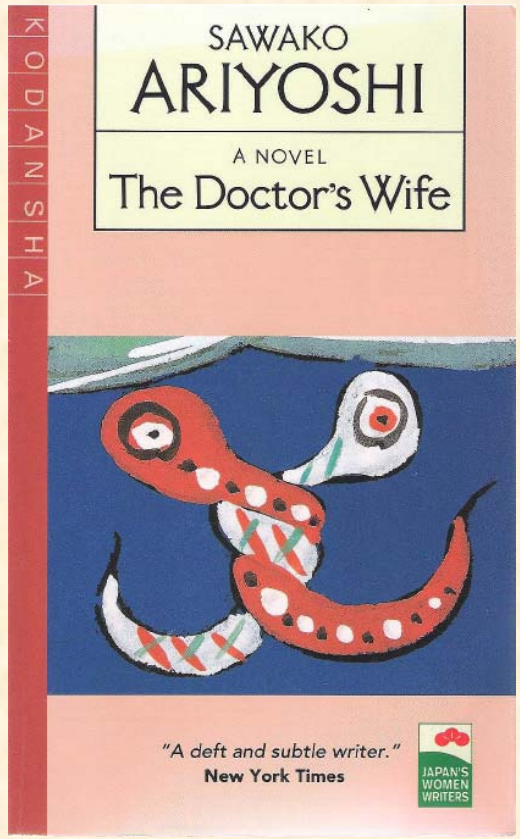
- Need for new drugs

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: LD_{50}/ED_{50}

  SAR and QSAR

Drug Development – Historical Outline

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

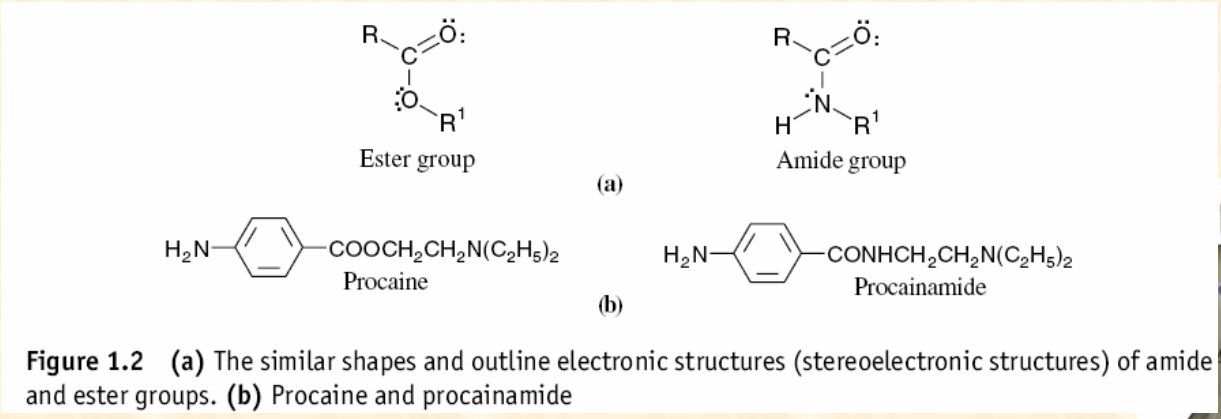
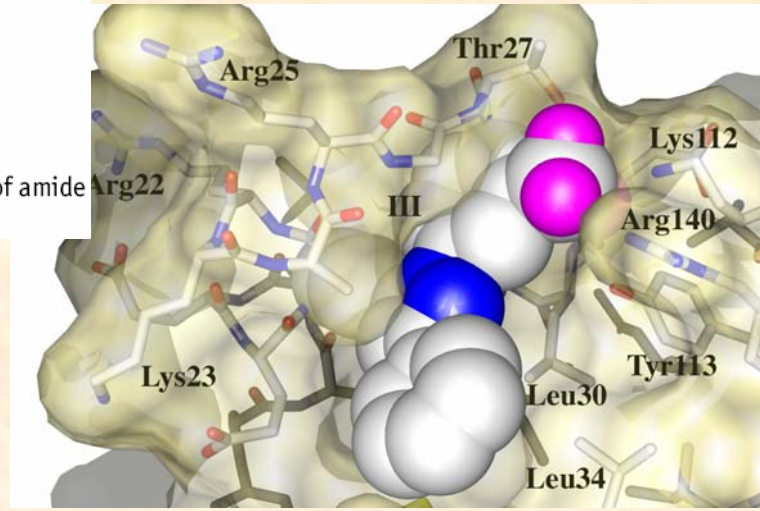


Figure 1.2 **(a)** The similar shapes and outline electronic structures (stereoelectronic structures) of amide and ester groups. **(b)** Procaine and procainamide

local anaesthetic

antiarrhytmic

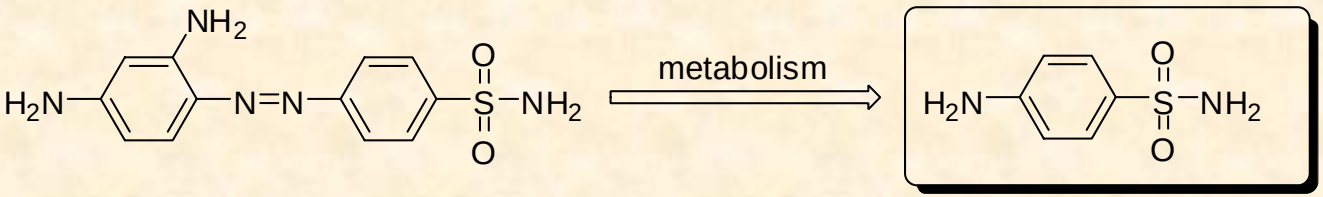


FBPase active site with inhibitor

Drug Development – Historical Outline

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

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



Prontosil Red

Sulfanilamide

- Modern drug development
  - Molecular modelling
  - Structural biology/biochemistry
  - Combinatorial chemistry/molecular libraries

Drug Development – Historical Outline

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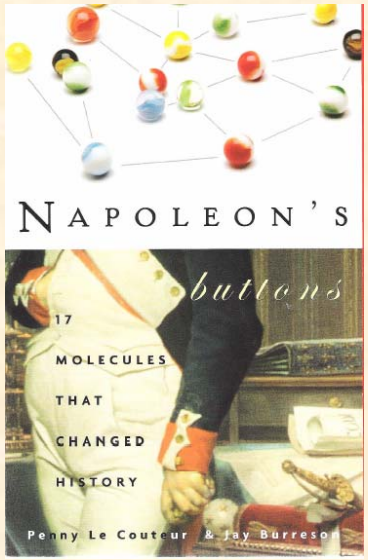
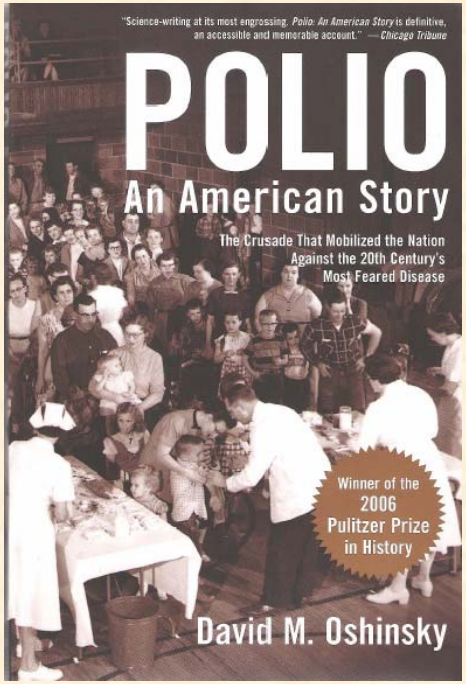
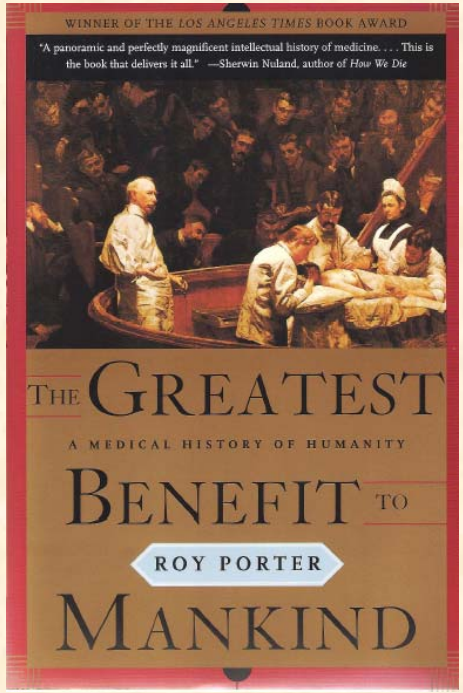
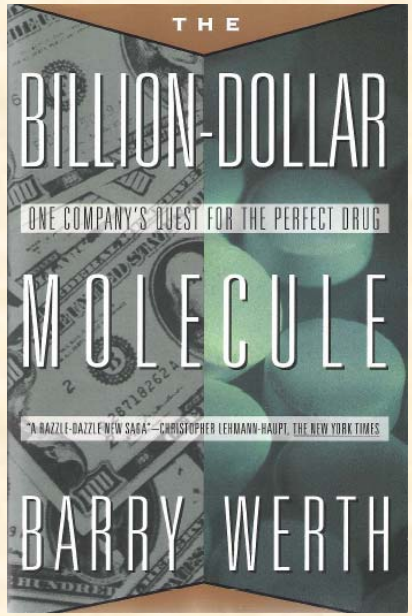
Further reading









Drug Development – General Stages

More teamwork based (different exertise), more structured (e.g The Pill) (but good luck is still welcome – Viagra)

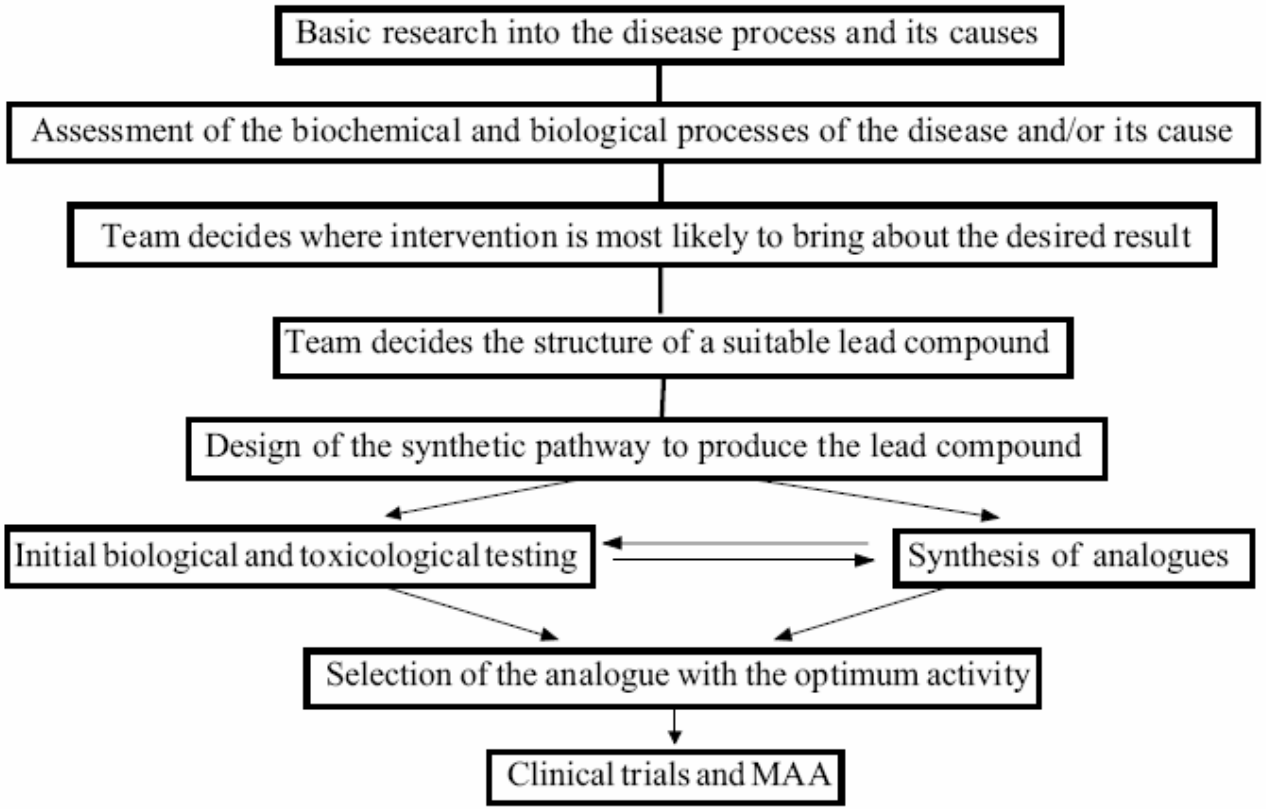


Figure 1.3 The general steps in the discovery of a new drug for a specific disease state

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

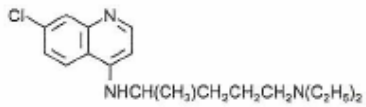
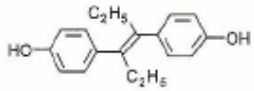
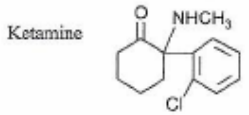
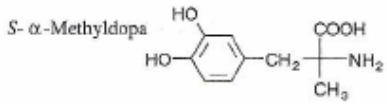
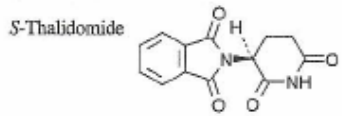
  Shelf life (usually 10% acceptable)

  After administration – long enough to reach target
  increasing stability – modifying structure
  more stable prodrug
  suitable dosage form

Drug Development – Leads and Analogues

Stability/activity of chiral drugs

Table 1.1 Variations in the biological activities of stereoisomers

First stereoisomer	Second stereoisomer	Example
Active	Activity of same type and potency	The *R* and *S* isomers of the antimalarial chloroquine have equal potencies 
Active	Activity of same type	The *E* isomer of diethylstilbestrol, an oestrogen but weaker, is only 7% as active as the *Z* isomer 
Active	Activity of a different type	*S*-Ketamine is an anaesthetic whereas *R*-Ketamine has little anaesthetic action but is a psychotic agent 
Active	No activity	*S*-α-Methyldopa is a hypertensive drug but the *R* isomer is inactive 
Active	Active but different side effects	Thalidomide: the *S* isomer is a sedative and has teratogenic side effects; the *R* isomer is also a sedative but has no teratogenic activity 

Drug Development – Leads and Analogues

Enhance *in situ* stability – inclusion complexes

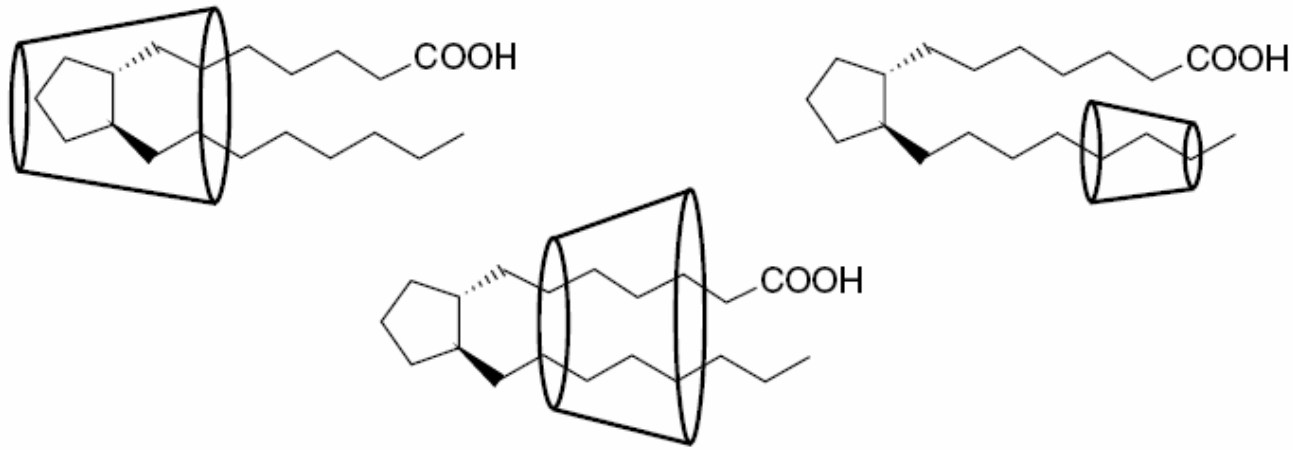
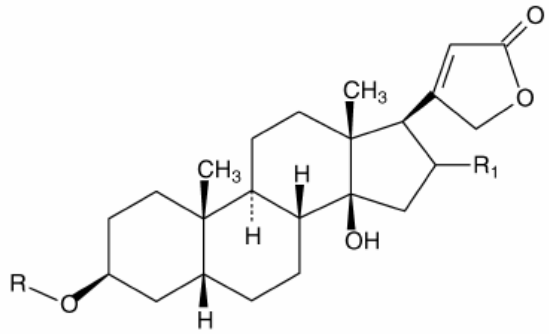


Figure 1.4 Schematic representations of the types of inclusion complexes formed by cyclodextrins and prostaglandins. The type of complex formed is dependent on the cavity size

Drug Development – Sources of Leads and Drugs

- Ethnopharmaceutical sources

Cinchona bark,
foxglove,
poppy fruit etc.



Key :
Digitoxigenin R_1 = H
Gitoxigenin R_1 = OH
Gitaloxigenin R_1 = OOCH

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 R, 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

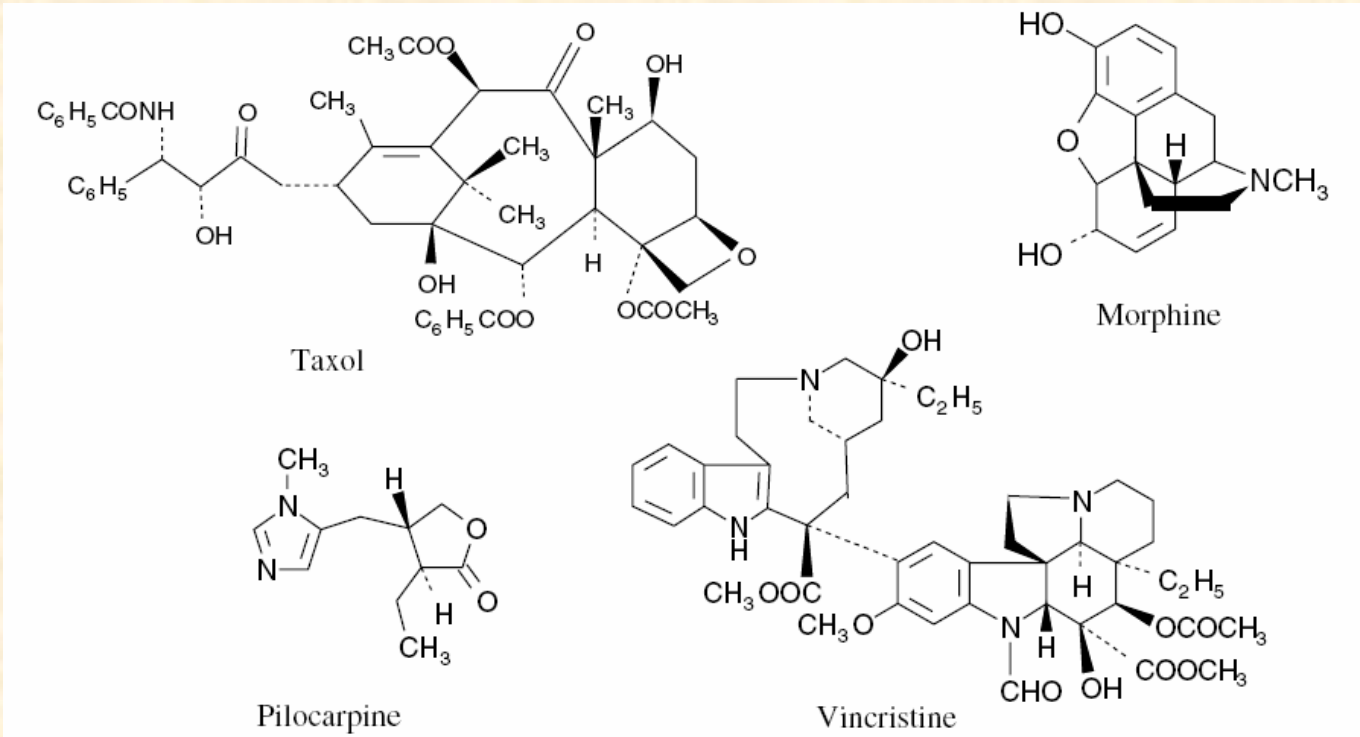
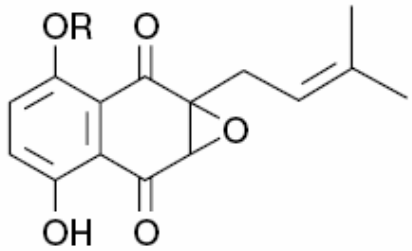


Figure 1.6 Examples of some of the drugs in clinical use obtained from plants. Taxol and vincristine are anticancer agents isolated from *Taxus breifolia* and *Vinca rosea* Linn, respectively. Pilocarpine is used to treat glaucoma and is obtained from *Pilocarpus jaborandi* Holmes *Rutaceae*. Morphine,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

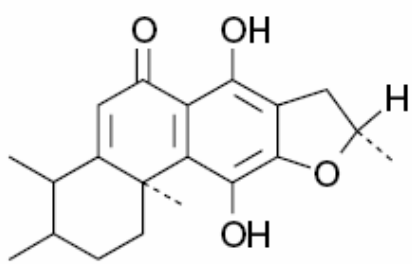
Drug Development – Sources of Leads and Drugs

- Plant sources

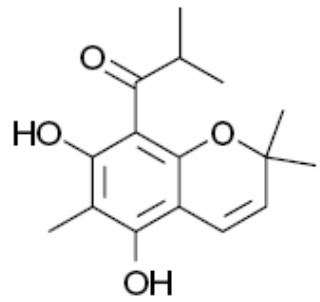
  Serendipity,
  or systematic
  search



A naphthoxirene derivative
Key: R = β-D-glucopyaranosyl



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

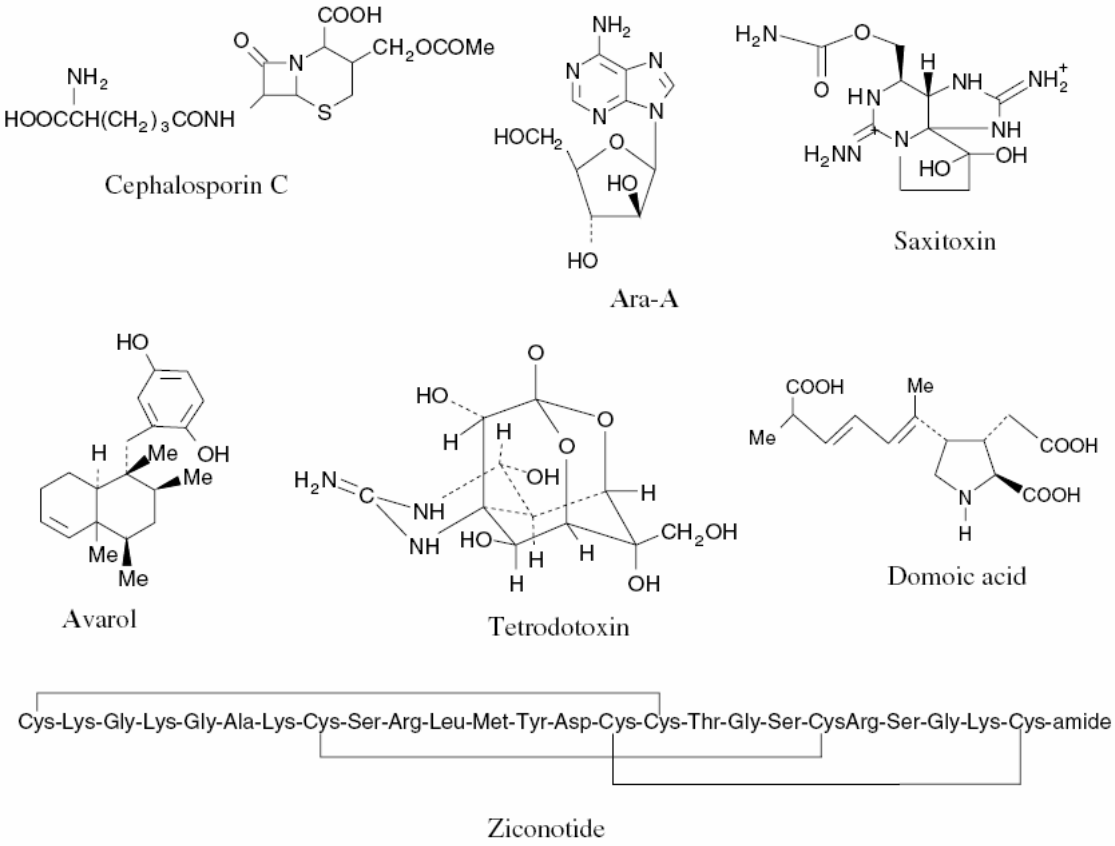


Figure 1.8 Examples of active compounds isolated from marine sources (Me represents a methyl group). Avarol is reported to be an immunodeficiency virus inhibitor. It is extracted from the sponge *Disidea avara*. The antibiotic cephalosporin C was isolated from the fungus *Acremonium chrysogenium (Cephalosporin 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 *Tetraodontiformis* 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

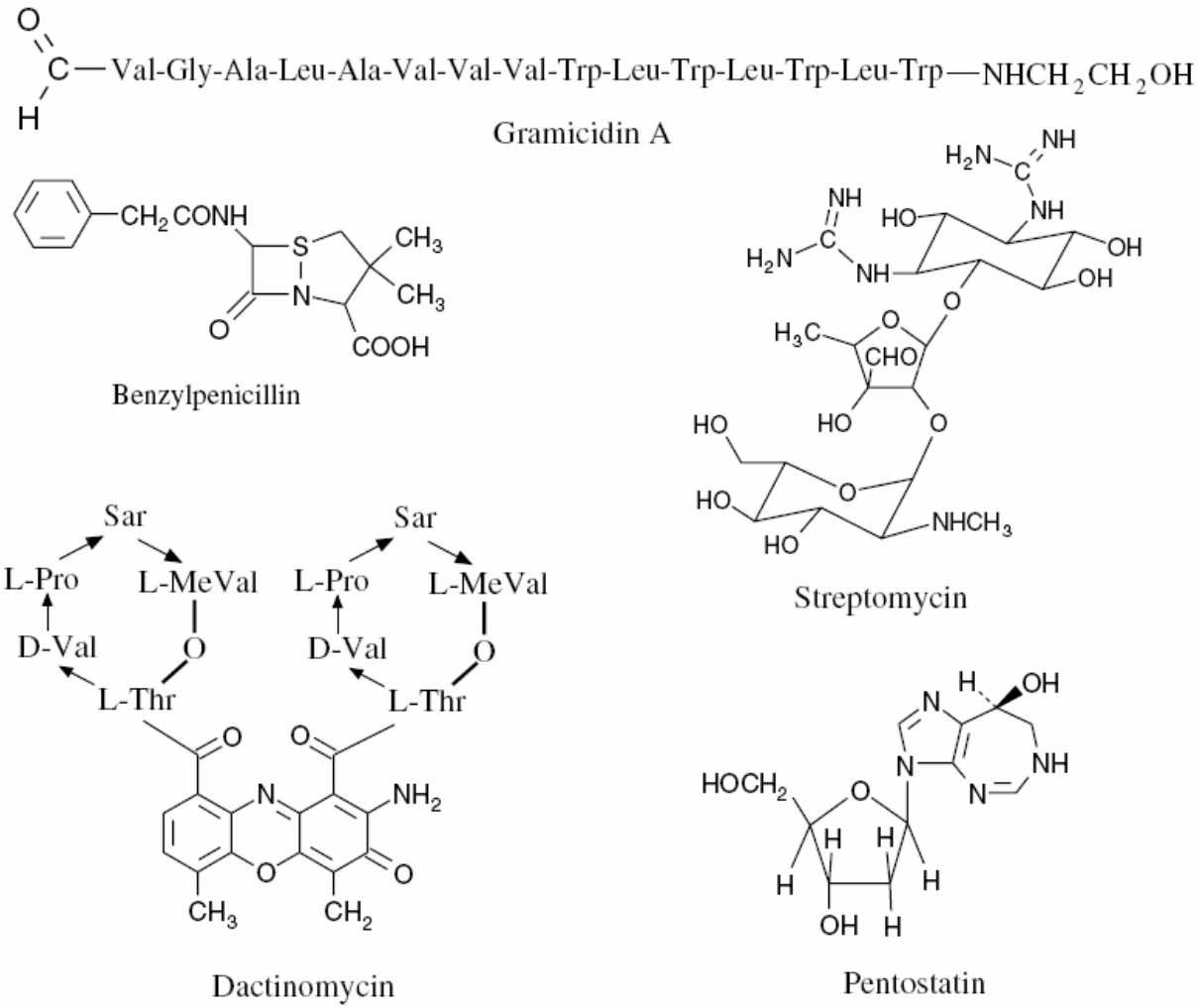
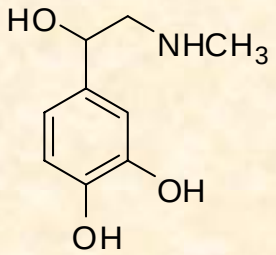


Figure 1.9 Examples of drugs produced by microbial fermentation. Gramicidin A, benzylpenicillin (penicillin G) and streptomycin are antibiotics isolated from *Bacillus brevis*, *Penicillin notatum* and *Streptomyces griseus*, respectively. The anticancer agents dactinomycin and pentostatin are obtained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

Drug Development – Sources of Leads and Drugs

- Animal sources - many hormones

Adrenaline – adrenal medullary extract



Insuline – 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

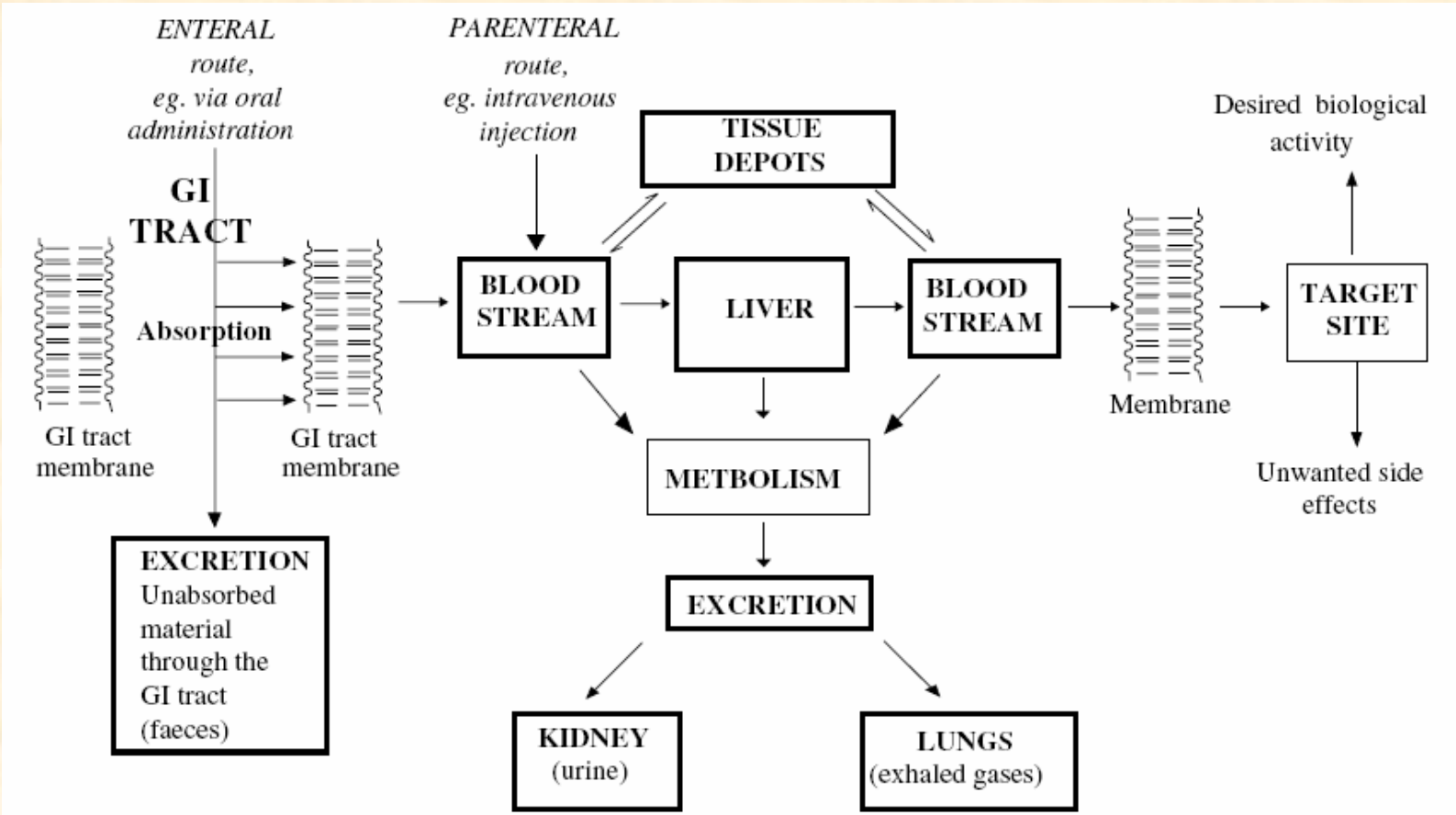


Figure 1.10 The main routes of drug administration and distribution in the body. The distribution of a drug is also modified by metabolism, which can occur at any point in the system

Drug Development – Administration

- Methods and Routes of Administration

Therapeutic window

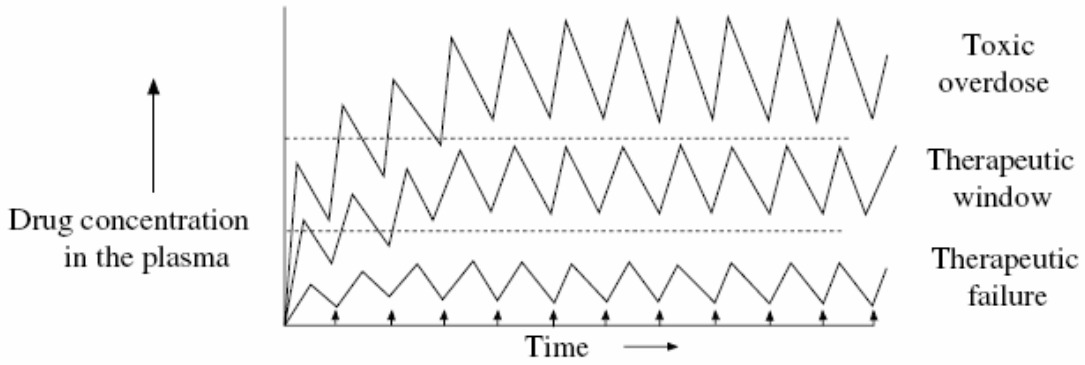


Figure 1.11 A simulation of a therapeutic window for a drug, given in fixed doses at fixed time intervals (↑)

Drug regimen : A dose and how it is administered

Pharmacokinetic properties: rate of absorption, distribution, metabolism, elimination from the body

Drug Development – Drug Action

- 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!

Drug Development – Drug Action

- 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)

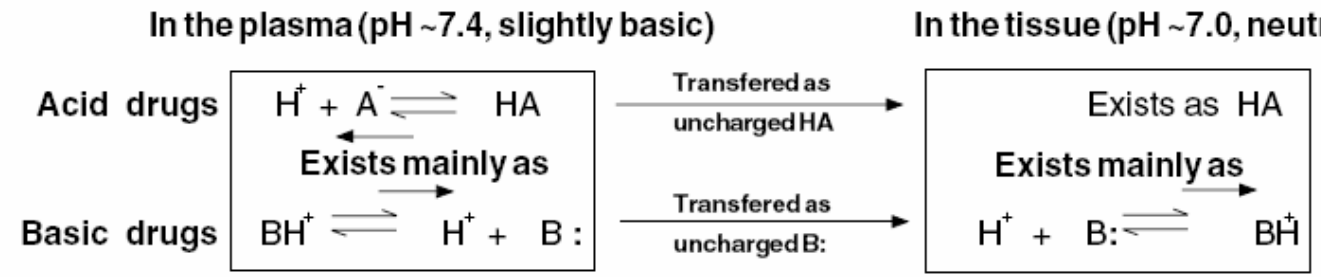
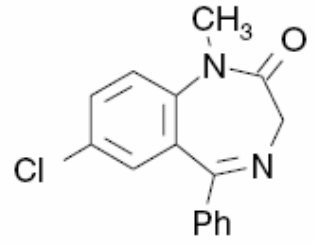


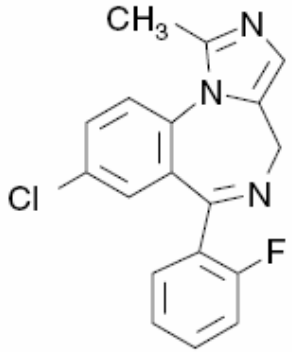
Figure 1.12 The species involved in the transfer of acidic and basic drugs from the plasma to the surrounding tissues

Drug Development – Drug Action

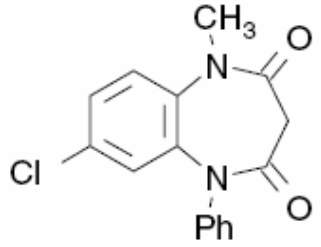
- Distribution
  blood-brain-barrier (BBB)



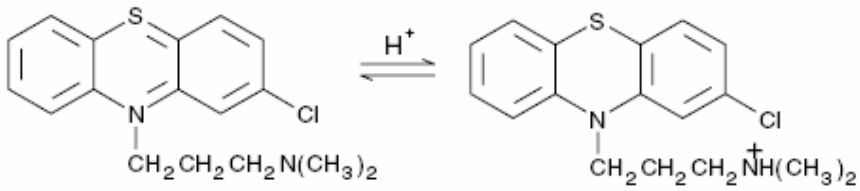
Diazepam



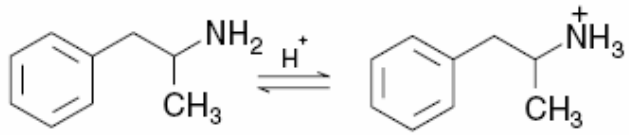
Midazolam



Clobazopam



Chlorpromazine



Amphetamine

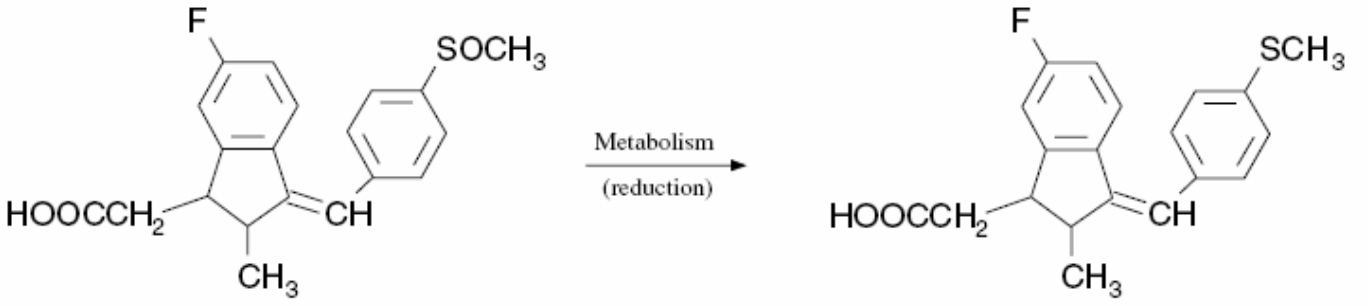
Figure 1.13 The structures of some of the drugs that are able to cross the blood–brain barrier

Drug Development – Drug Action

- Metabolism

  the biotransformation of drugs into other compounds (metabolites) - mainly in the liver

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



Inactive administered form of the drug

Active sulphide metabolite of the drug

Sulindac

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

Drug Development – Drug Action

- Metabolism

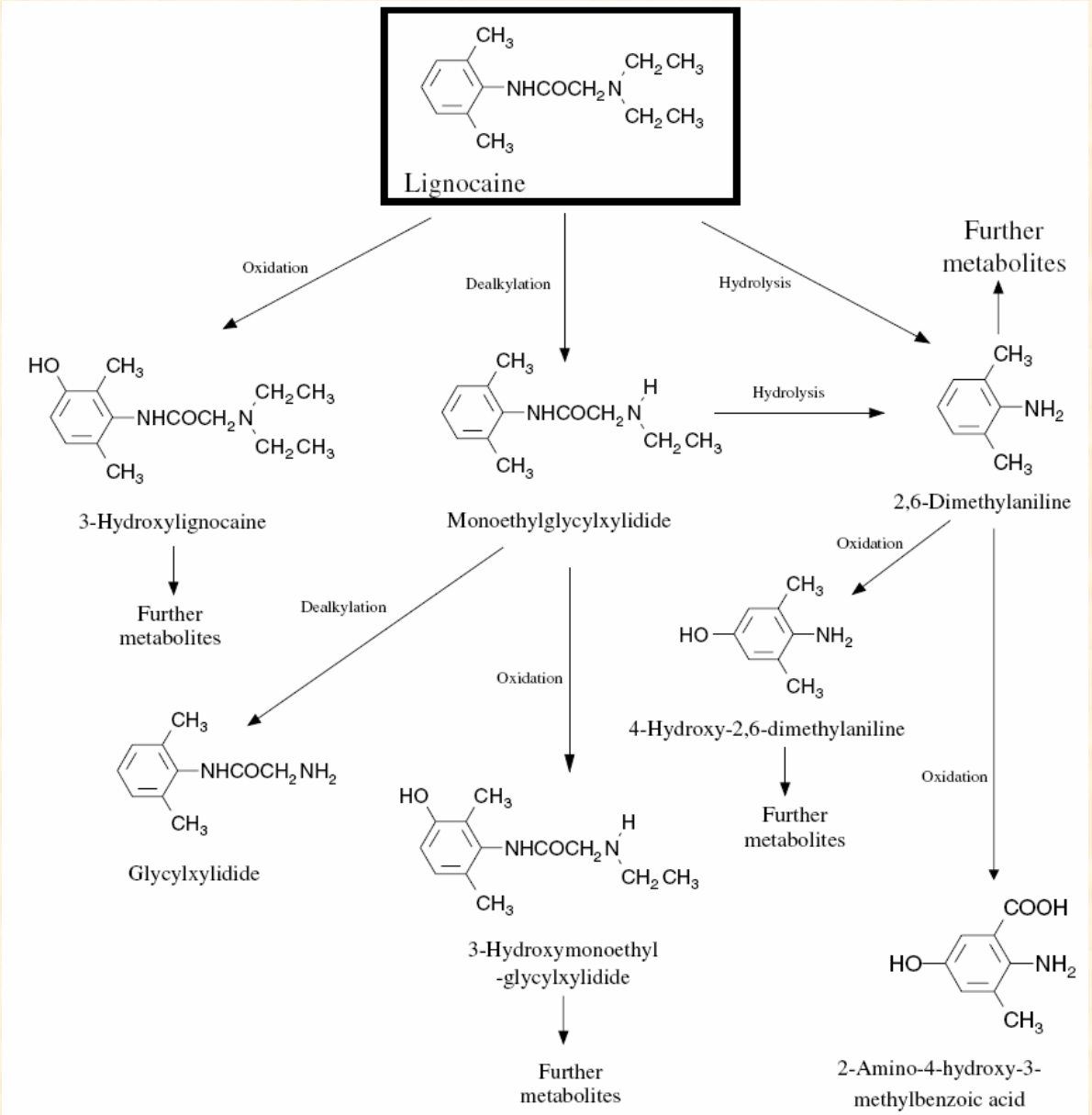


Figure 1.14 An outline of the known metabolic pathways of the local anaesthetic lignocaine

Drug Development – Drug Action

- 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*

Drug Development – Drug Action

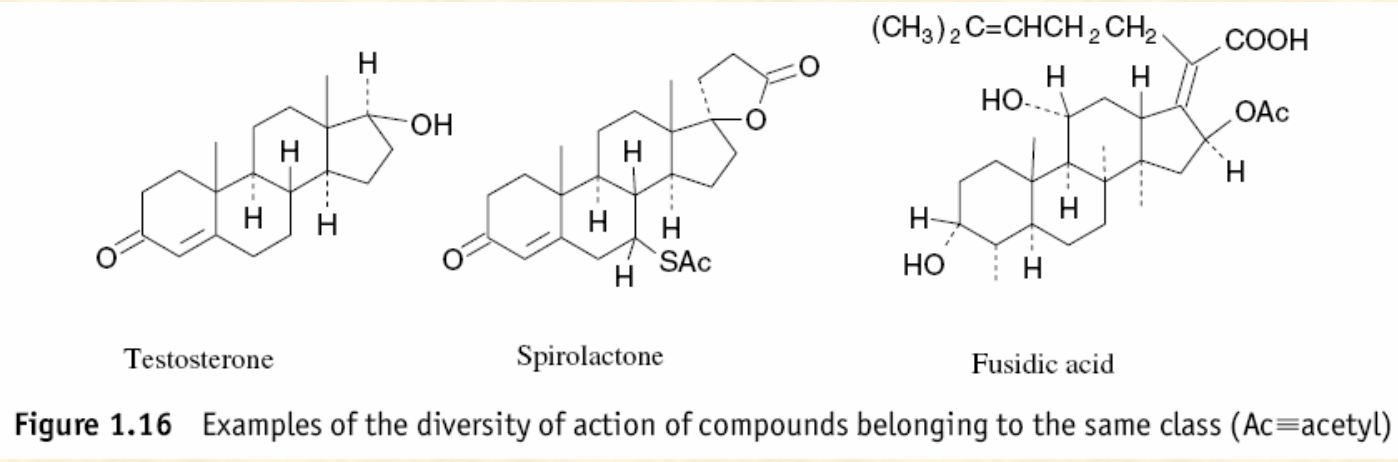
- Lead optimization and ADME

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



Testosterone Spirolactone Fusidic acid

Figure 1.16 Examples of the diversity of action of compounds belonging to the same class (Ac≡acetyl)

- Pharmacological action

  diuretics, hypnotics, vasodilators, respiratory stimulants etc.

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

Drug Development – Prodrugs

- Inert compounds that are converted by enzymes active drugs

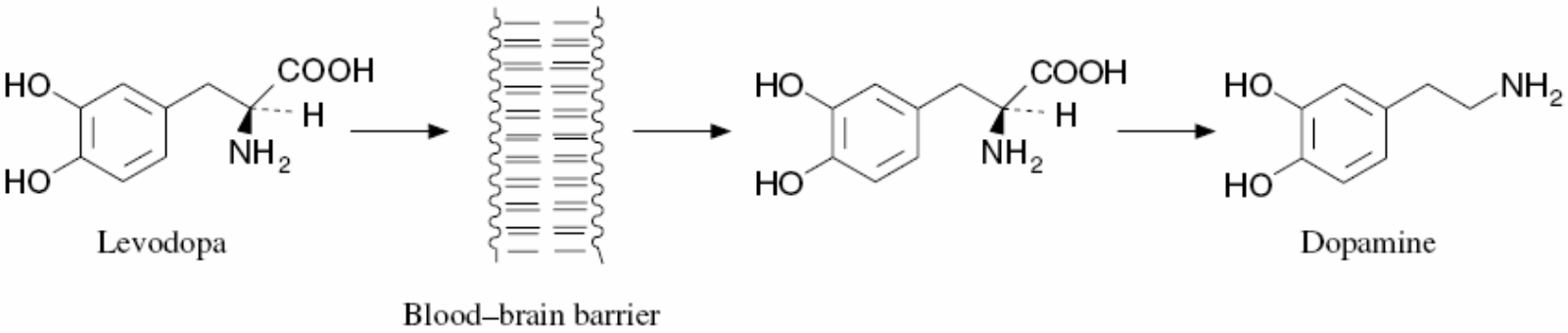


Figure 1.17 A schematic representation of the formation of dopamine from levodopa